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Aspen, Colorado
June 13, 14, 15, 1958

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Sponsored by
Colorado Tuberculosis Association
Colorado Trudeau Society
University of Colorado School of Medicine
Colorado Foundation for Research in Tuberculosis
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FOREWORD

Although pulmonary emphysema is a widely applied diagnosis, the condition itself is poorly understood and, even among the experts, there is lack of agreement on almost every point that would characterize the disorder anatomically, functionally, and clinically. The need for a universally acceptable concept of pulmonary emphysema has become pressing in recent decades due to the increased incidence of the disease and the fact that it exhibits an ominous parallel to the progressive modernization of our environment.

To some, pulmonary emphysema is already a public health problem in America. Emphysema is, even now, a very serious matter in Great Britain, where it is a prominent feature of the chronic bronchitis syndrome which has overtaken every other pulmonary disease as the foremost crippler and killer.

National mortality statistics in the United States show that the geographic frequency of emphysema is proportionate to the degree of urbanization: it occurs twice as commonly in our cities as in our rural areas. In interpreting this relationship, it is the consensus of many authorities that, while many influences inherent to civilization no doubt play a part, atmospheric pollution is a factor of primary significance.

The Air Pollution Medical Program of the Public Health Service, whose objective it is to study the health implications of atmospheric pollution, seeks to identify those diseases that in some way may be caused by or be related to it. Pulmonary emphysema, thus, is of particular interest to us; and we are aware of the necessity for its adequate epidemiologic assessment. Such assessment, however, will be feasible only after we possess a clearer understanding of the characteristics that define emphysema.

Since the information gathered at the First Aspen Conference on Research in Emphysema should add materially to that understanding, the Air Pollution Medical Program of the Public Health Service is pleased to have assisted in making these Proceedings more widely available.

March 18, 1959

RICHARD A. PRINDLE
Chief, Air Pollution Medical Program
Division of Special Health Services
Department of Health, Education, and Welfare
Public Health Service
Washington, D. C.

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INTRODUCTION

DR. BEN EISEMAN (Denver, Colorado): I would like to introduce Dr. Zarit, President-elect of the Colorado State Medical Society.

DR. JOHN ZARIT (Denver, Colorado): Leading scientists throughout the United States, Canada, and Australia are here today for the first Conference on Research in Emphysema. Attending the conference are anatomists, pathologists, veterinarians, clinicians, pulmonary physiologists, and individuals doing special research in elastic tissue and in aerodynamics in relation to pulmonary function. The purpose of the conference is to clarify the terminology and explore the etiology and pathogenesis of emphysema so that we can define emphysema, to report recent progress in emphysema research, to test the area of future research, to help integrate the contributions of others in the field of anatomy and veterinary medicine.

We are sorry that the Dean of Pulmonary Physiology is not with us. To some of us he was a teacher; to others he was a continuing stimulus in the field of research in pulmonary physiology. I refer to the late Dr. Henry Sewall, whose memory I hope will be with us during the three days of our deliberation.

It seems to me that the challenge of the disability resulting from emphysema can be met in one of two ways: either by learning to master the entire disease or, if this is not possible, to teach the patient to live his life to the fullest with this disease.

My challenge to you is that we be granted (*1*) "the serenity of accepting what we cannot change," (*2*) "the courage to change the things we can change," and (*3*) "the wisdom to know the difference."

THEORIES OF THE PATHOGENESIS OF EMPHYSEMA[1]

ROGER S. MITCHELL

The Conference Steering Committee has identified three general purposes of this conference: (*1*) to exchange information on the available knowledge and our lack of knowledge regarding the etiology and pathogenesis of diffuse obstructive pulmonary emphysema, hereinafter called "emphysema." Numerous scientific disciplines are involved, including anatomy, pathology, biochemistry, physiology, embryology, biophysics, clinical medicine, and veterinary medicine; (*2*) to clarify terminology as it pertains to emphysema and related problems; (*3*) to endeavor to stimulate interest and research into the etiology and pathogenesis of this obscure and common disorder.

Parenthetically, I believe we are all agreed that we are not here to discuss *therapy* except insofar as it may throw some light on the cause.

It is very important at the outset to agree, if possible, on what we mean by "emphysema." For instance, localized blebs and bullae are called "emphysema" by the radiologist, surgeon, and pathologist. These lesions may be—but often are not—associated with the generalized disease with which we are principally concerned here. Patchy areas of alveolar thinning, dilatation, and rupture, plus bronchiolar ectasia and fibrosis, occur in foci of coal workers' pneumoconiosis, healed tuberculosis, fungal diseases, and other pulmonary infections; these are often described as focal "emphysema" by pathologists.

Patchy and sometimes extensive alveolar damage of this kind usually accompanies the pulmonary fibrosis found in association with silicosis, sarcoidosis, and Hamman-Rich disease; this is also labelled "emphysema." Overdistension of lung consequent upon removal or collapse of other portions of lung is often called "emphysema" or "compensatory emphysema" by radiologists and clinicians.

It seems important, in other words, to emphasize that these and perhaps other types of so-called "emphysema" appear essentially to be patchy, localized, *secondary* to some other morbid process, and not the principal subject to be discussed here.

We should recognize, however, that consideration of focal emphysema, especially when traceable to a known cause, may be shown to be the precursor of diffuse emphysema, and may concern us because of the light it may throw on the pathogenesis of the generalized process.

The following definition or description of emphysema is offered as one point of departure for our discussions.

Diffuse obstructive emphysema may be defined as a chronic, usually progressive, disorder of the lungs which may accompany other lung diseases, but frequently occurs alone. *Pathologically* it is characterized by dilated, thinned, and often ruptured alveoli, bronchiolar obliteration and ectasia, bullae (especially on the surfaces of the lungs), fibrosis, impairment in pulmonary vasculature, right ventricular hypertrophy and often dilatation, and no general agreement on the finding of clear-cut gross or microscopic evidence of the airway obstruction so predominant clinically. Chronic bronchial and bronchiolar infection, usually patchy, is often found. *Physiologically* it is characterized by an absolute and relative increase in residual volume, an increase in the work of breathing, and marked diminution in ventilatory, gas mixing, and diffusion capacities, and (late in the course) evidence of pulmonary hypertension. *Roentgenographically* it is characterized by large bright lung fields with a paucity of peripheral vascular markings, increased anteroposterior diameter of the chest, high clavicles, "squared-off" apices, low, flattened hemidiaphragms with impaired excursion, occasional bullae, impaired ventilation (noted particularly on expiration by fluoroscopy), and right heart enlargement. *Clinically* it is characterized by dyspnea on exertion unexplained by other findings, a frequent but not invariable history of cough prior to the onset of dyspnea, interference with movement of air out of and, to a lesser extent, into, the lungs (usually but not always a progressive course), and the frequent ultimate development of right heart failure. Finally and most notably, a *poor correlation* among the findings from these four disciplines is well recognized.

Many of the clinical manifestations of emphysema seem to merit a search for an answer, since the search may very well point the way to productive laboratory or clinical research. Is emphysema frequently associated with peptic ulcer and, if so, is this association related to carbon dioxide retention? Why do some patients show carbon dioxide retention and/or polycythemia as an early

[1] From the Colorado Foundation for Research in Tuberculosis, Denver 20, Colorado.

or predominant manifestation of the disorder while others do not? Just how frequently does emphysema complicate true bronchial asthma? Is *bronchospasm* an important factor early in the course of emphysema? If chronic bronchial and bronchiolar infection can lead to emphysema, why cannot emphysema result from other causes of bronchiolar narrowing, i.e., spasm? What is the explanation of the wide variation in the response of the pulmonary circulation and of the right heart to the insult of emphysema in different individuals? Why is emphysema ten to twenty times more common in men than in women in some areas, e.g., Denver, and only three to four times more common in men in other areas, e.g., London? Is the lower ratio reported by the British a reflection of exposure to industrial smog and inclement weather? Does the female with emphysema usually give a prior history of asthma or bronchiectasis, in contradistinction to men? Are these emphysematous females hormonally more like men than are other women?

How do we account for the wide variations in the course of emphysema? Some become ill quite abruptly and others very gradually; some progress in a malignant fashion to an early death from respiratory insufficiency and oxygen lack, on the one hand, or right heart failure, on the other; while others become disabled gradually and may reach a plateau and live on for many years in a state of moderate chronic disability. Is the obvious obstruction to airflow due to collapse of bronchi or bronchioles which have been weakened by a primary cartilagenous or elastic tissue disturbance, or due to impairment of ciliary action? (For instance, sulfur dioxide, a common contaminant in industrial fumes, is capable of causing temporary paralysis of ciliary action. Cadmium fumes are reported to cause "pulmonary emphysema" with traces of the metal to be found in various tissues.) Is so-called "senile" emphysema, usually manifested by rather marked physical findings but with relatively mild symptomatology, an entity; if so, does its existence indicate that at least one etiologic factor involved in the disorder in all persons is loss or disturbance of pulmonary elastic tissue, perhaps attributable to accelerated aging?

Why do most emphysematous persons note marked loss of weight—often from one-sixth to one-fourth of their total body weight—with the onset of severe pulmonary disability, whereas a few with a comparable disability lose no weight at all? Are the latter those with a history of asthma or those with polycythemia?

Is emphysema commonly associated with exposure to industrial smog, tobacco smoke, and dust? Is "bronchitis," as the British use the term, partially or wholly synonymous with "emphysema" as we use the term? Why do altitude, humidity, and temperature have such a variable effect upon emphysematous persons?

Can emphysema be produced with regularity in an experimental animal? By what method? Is it emphysema as we know it in man? Does emphysema occur naturally in the horse, dog, or other animals? Is hard laborious physical work associated with emphysema, as appears to be a fact in the presumably emphysematous, "windbroken" or "heavey" horse? How can we use such animals profitably as experimental subjects? Is emphysema associated in any way with the "brisket disease syndrome" of cattle, which is a form of right heart failure quite regularly adversely affected by high altitude and relieved by descent to lower altitudes?

What is the epidemiologic picture of emphysema in various geographic locations? Is the incidence of emphysema affected by population density, industrial or other air pollution, weather, or geography? Is emphysema increasing in frequency?

Is it not true that the term emphysema is a common wastebasket used by clinicians for patients with dyspnea and/or right heart failure that do not fit easily into some standard category? Do we have a simple, reliable screening test with which to discover emphysema early and, if so discovered, can we arrest its progress by any means?

For purposes of review and to help organize our thinking on the etiology and pathogenesis of emphysema, many of the etiologic theories presently entertained are listed:

1. *Chronic recurrent bronchiolar infection* appears to be the most widely accepted hypothesis advanced to date. It includes the belief that air passages beyond an obstructed bronchiole can remain aerated by "collateral ventilation" and that, as a consequence, air enters more freely than it leaves an involved area.

2. Chronic trauma due to *severe coughing*, consequent upon impairment of the flow of mucus and removal of detritus, is stressed as a common contributing cause.

3. Inflammatory swelling of bronchiolar mucosa and/or *impairment of ciliary action*, brought on by the inhalation of *tobacco* smoke, *smog*, or other *irritant industrial fumes* are thought to play a role.

4. Does *premature aging* or some other derangement of the pulmonary or bronchial *elastic tissue* or of the *tracheobronchial cartilages* play a part? The latter defect is postulated in part because of the endoscopic observation that the trachea and visible bronchi collapse upon forced expiration more easily in emphysematous patients than in those without emphysema. "Lobar emphysema" of infants has also been ascribed to a congenital defect of tracheobronchial cartilage.

5. A primary disorder of the pulmonary or *bronchial circulation* has been postulated, with the ventilatory and respiratory disorders presumed to come on later or secondarily. It seems very likely that the reverse occurs.

6. A *structural disorder of the thorax* is often associated with emphysema. Can this ever be the primary defect, as it may be in *kyphoscoliosis*, secondary in turn to poliomyelitis or tuberculosis of the spine?

7. Some *hormonal disorder* is suggested by the heavy preponderance of the disease in males.

8. The possibility of an *hereditary tendency* must be entertained.

In conclusion, it is altogether probable that emphysema may prove to be a *syndrome* with several *different* and probably *overlapping* causes.

ANATOMY

BEN EISEMAN, *Moderator*

PRE- AND POSTNATAL DEVELOPMENT OF THE RESPIRATORY PORTION OF THE HUMAN LUNG[1,2]

With Special Reference to the Elastic Fibers

CLAYTON G. LOOSLI[3] AND EDITH L. POTTER

INTRODUCTION

The pre- and postnatal development of the human lung is not completely understood. The problems of pulmonary development in man are not answered by studies of lung structure and growth in experimental animals (1, 2), although such studies are obviously helpful.

W. S. Miller (3) dominated the thinking concerning the structure and development of the human lung in this country for more than fifty years. The writers are not aware of published studies which he might have made on the prenatal development of the lung in man. However, on page 73 of the second edition of his monograph, *The Lung*, he states in the third paragraph that:

> In the fetal lung the pulmonary alveoli are lined by a continuous layer of cuboidal epithelium. As respiration becomes established and the alveoli distend, the epithelium still continuously becomes stretched out so thin that the usual laboratory methods fail to demonstrate it.

With the use of the electronmicroscope, Low (4) demonstrated a thin cytoplasmic membrane covering what appear to be bare capillaries by the usual laboratory methods. However, the origin of the cells, whose cytoplasmic expansions cover the capillaries, is still in question and a subject of study by several investigators who are competent in the use of electronmicroscopic procedures (*see* 36, 37).

Numerous studies on the development of the human lung have been made by several groups of investigators in this and other countries (5–16). All investigators recognize the gradual intrauterine development of the lung as it changes from a glandular to a highly vascular organ. Most recognize that the lung at birth is still incomplete as far as that seen in the adult is concerned (8, 9, 12, 14–16). Likewise, several excellent studies have been made concerning the development of the elastic fiber tissue in the pre- and postnatal human lung (17–29). Dubreuil and associates (8, 9) and Engel (14) have emphasized the importance of the elastic fiber system in the respiratory portion of the lungs in determining their stages of development in the human fetus.

The problem of the terminology of the final units of the respiratory portion of the lung has been the subject of much study and discussion. Reviews on this subject have been written by Miller (3), Engel (14), and Grethmann (30). Hayek (31) and Krahl (32, 33) have reviewed current concepts of the finer structure of mammalian lungs. Both conclude that many problems remain unsettled and require further investigation.

The present study of the pre- and postnatal human lung with respect to the development of the elastic fiber system and alveoli is designed to help answer some of the problems of the histology, pathology, and physiology of this organ.

MATERIALS AND METHODS

Ninety-seven prenatal and 14 postnatal lung specimens were employed in this study. They were selected for their good state of preservation. Thirty-one of the prenatal group were stillborn while 66 lived for twenty minutes to three weeks (table 1). The postnatal group varied in age from one month to twenty-seven years (table 2).

The lungs were fixed in 10 per cent neutral formalin or 10 per cent Zenker-formol solution for ten to twenty-four hours. The lobes of some of the fetal specimens were fixed intrabronchially in

[1] From the departments of Medicine, Obstetrics, and Gynecology, University of Chicago School of Medicine, Chicago 37, Illinois.

[2] Supported in part by a Special Fellowship Award of the Commonwealth Fund and the Women's Auxiliary of the Endowment for Cancer Research of the University of Chicago.

[3] Present address: University of Southern California School of Medicine, Los Angeles 33, California.

TABLE 1

PRENATAL SPECIMENS OF HUMAN LUNG

Group	Number of Specimens	Weight	Weeks of Gestation	Number Stillborn	Number Who Breathed
		gm.			
1	6	30–345	9–16	6	0
2	6	350–380	17–21	2	4
3	6	430–500	22–27	0	6
4	5	565–650	25–28	2	3
5	5	670–700	23–28	2	3
6	15	700–850	25–32	3	12
7	5	870–980	27–29	2	3
8	9	1,000–1,200	26–33	0	9
9	9	1,250–1,550	30–33	2	7
10	7	1,850–2,200	34–43	4	3
11	11	2,240–2,850	36–42	3	8
12	13	3,000–5,840	38–40	5	8
Total	97			31	66

TABLE 2

POSTNATAL LUNG SPECIMENS

Group	Number of Specimens	Age
1	2	1 month
2	2	3 months
3	2	6 months
4	4	10–12 months
5	1	5 years
6	1	12 years
7	1	18 years
8	1	27 years

order to compare the expanded lung with the normally collapsed ones. Most postnatal specimens were fixed by immersion of small sections in the fixative. The lungs of the 12-, 18-, and 27-year-old subjects were fixed intrabronchially.

After fixation the lungs were washed, dehydrated in alcohol, and embedded in paraffin. Serial sections, 7 to 10μ in thickness, of blocks were made from each expanded and collapsed lobe. One was stained with hematoxylin-eosin, and one with hematoxylin-eosin-azure II for cellular detail; one with orcein for elastic fibers, and one with Mallory's azan (azocarmine analine blue-orange G) for collagenous fibers and connective tissue. These procedures have been employed by one of us (C. G. L.) for studying the structure of the lungs in a variety of experimental animals over a period of several years (1, 2).

The observations in the present study are presented in chronologic order in relation to the age or weight of the fetal and postnatal specimens. Space does not permit illustrating adequately the development of the elastic fiber system in the pleura, interlobular connective tissue, and vessel walls. However, reference will be made to the development of elastic fibers in these structures. Emphasis is placed on the development of the elastic fiber tissue in the walls of the terminal bronchioles and respiratory portion of the lung in relation to the development of the respiratory unit, the pulmonary acinus with its alveolar ducts, sacculi, and alveoli. Illustrations have been selected from lungs expanded with fixative, for they demonstrate more adequately developmental changes in the lung as it changes from a glandular to a vascular organ.

OBSERVATIONS

At three months of gestation the lobes of the lungs were well demarcated (Plate I *A*). Cartilage was present in the trachea and main stem bronchi. Elastic fiber bundles were present in the walls of the trachea and main stem bronchi, pulmonary artery, and pleura. They were also present in the walls of the smaller arteries accompanying the main stem bronchi. At three months' gestation the lung had the appearance of a glandular organ showing branching epithelium-lined channels growing in lobular fashion in dense mesenchymal tissue (Plate I *A*).

This appearance continued for another two months' gestation, branching epithelium-lined tubules becoming more complex. At four months' gestation, spaces which were to become bronchi could be detected by the deeper staining of the epithelial cells. Compared to those in the growing end buds of the tubules (Plate I *B*), these older epithelium-lined spaces usually appeared in the center of the lobules. Wherever the epithelial cells stained deeply, elastic and collagenous fibers appeared in the subepithelial tissue. There was also the associated artery which had well-developed elastic fibers in its walls (Plate I *B*).

At five months the primitive air spaces continued to show a lining of epithelial cells. Expansion of the spaces with fixative resulted only in flattening of the cells to varying degrees (Plate II *A*). Elastic fibers were well developed in the pleura, vessels, and bronchial walls. At points where the walls projected into the lumina of the epithelium-lined spaces, cross-sections of deeply staining elastic fiber bundles could be seen (Plate V *A*). Up to this time the mesenchymal tissue showed essentially no vascularization.

At five and one-half to six months, the lung began to lose its glandular appearance (Plate II

B). The epithelial cells lining the bronchial tubular system stained deeply with the hematoxylin-eosin-azure II procedure. The tubules which were to become the respiratory portion took the stain less deeply. Vascularization of the mesenchymal tissue began in association with the development of the elastic fibers and immediately subjacent to the epithelial cells. At many points along the walls of the future spaces, developing capillary loops grew between the epithelial cells to separate them into groups. No overlying cytoplasmic expansions of the epithelial cells lying adjacent to a protruding capillary could be seen.

From six to seven and one-half months, further differentiation of the lungs took place. The expanded lungs showed the respiratory lobules to be simple branching channels leading from the terminal bronchioles (Plate III). The walls of the channels were irregular in thickness and showed sharp projections into them. Inspection of these lungs with appropriate stains revealed a marked further development of elastic fibers and blood capillaries in the channel walls. The elastic fiber bundles were located at the tissue points which projected into the channel spaces (Plate V *B*). In the same way, capillary loops were associated with these projections. They appeared to be exposed directly to the air spaces and lay on the elastic fiber bundles (Plate V *B*). In Plate VI *A*, the position of the elastic fiber bundles is shown in the same but expanded lung illustrated in Plate V *B*. The shallow evaginations between the elastic fiber bundles show groups of cuboidal epithelial cells and represent probably primitive alveoli.

Plate VI *B* is the expanded lung section of a six-and-one-half month fetus which lived eight days. No definitive alveoli are present, but numerous cross-sections of elastic fiber bundles may be seen at points along the thick walls of the expanded channels. There is marked vascularization of the tissue, numerous capillary loops appearing to lie directly exposed to the channel spaces.

At seven to seven-and-one-half months' gestation elastic fibers in the pleura, blood vessels, and bronchi were well developed (Plate VII). In the connective tissue of the walls of the respiratory portion of the lungs they were present only at the tips of the tissue which projects into the channel spaces. The evaginations between these projections might be considered primitive alveoli. In these specimens, as in earlier ones, the blood capillaries developed at the points on the walls where the elastic fibers appeared. They lay between the elastic fiber bundles and the lumina of the channels.

From seven-and-one-half months until term, there was further differentiation of the respiratory portion of the lung into a vascular organ. This was associated with the further development of the respiratory channels into alveolar ducts which processed small but definitive alveoli (Plates IV and VIII). In the collapsed lung of the term fetus (Plates IV *A* and VIII *A*), it was difficult to make out the different components of the respiratory lobules. By expansion with fixative (Plates IV *B* and VIII *B*), the branching alveolar ducts with small, shallow alveoli were clearly seen. In such lungs the glandular appearance had been replaced by that of a highly vascular organ, blood capillaries being the most conspicuous feature of the walls of the alveolar ducts and alveoli. The architecture of the walls of the terminal bronchioles with their connecting alveolar ducts is clearly delineated and shown in the expanded lung stained for elastic fibers (Plate VIII *B*). As in previous specimens, the elastic fiber bundles are confined to the tips of the walls of the shallow alveoli around their openings. The substance of the alveolar walls did not contain elastic fibers at this stage of development. Respiratory bronchioles with alveoli in their walls were not seen in fetal lungs at any stage of prenatal development.

In the lungs of the term fetus, residual epithelial cells which once lined the primitive air channels were rarely seen. Yet in none of the preparations in this prenatal series was there evidence that they were lost by degeneration and desquamation. The formation of alveoli appeared not to be dependent on their continued presence, at least in conspicuous numbers.

The respiratory lobules in the human lung continued to develop following birth. The alveolar ducts and alveoli gradually became larger and longer over a period of several years. This was seen by comparing the size of alveoli in the lungs of the term fetus (Plate VIII *B*), a 9-month-old infant (Plate IX *A*), a 5-year-old child (Plate IX *B*), and a 12-year-old child (Plate X *A*). These lungs were all fixed in approximately the same state of expansion. The photographs are essentially the same magnification. The elastic fiber tissue increased in amounts as the lung grew, but up to 5 years of age it was essentially confined

to the openings surrounding the mouths of the enlarging alveoli (Plate VIII *B*; Plate IX). Occasionally, small segments of elastic fibers could be seen extending along the walls of the alveoli.

In the lung of the 12-year-old child, the alveoli and alveolar ducts (Plate X *A*) are many times larger than those seen in the lungs of the term fetus (Plate VIII *B*) and of the 9-month-old infant (Plate IX *A*). In the lung of the 12-year-old child, the elastic fibers were not yet well developed in the walls of the alveoli or alveolar ducts. This was in contrast to the lungs of an 18-year-old male youth (Plate X *B*). As seen in Plate X *B*, heavy elastic fiber bundles not only surround the mouths of the alveoli but extend in a branching fashion through the alveolar walls themselves. A similar quantity and distribution of elastic fiber tissues were seen also in the lungs of a 27-year-old male.

Discussion

The importance of the elastic fiber system in the lung in determining the developmental stages of the components of the respiratory units is emphasized in this study. Dubreuil and associates (8, 9) and Engel (14, 15) have previously recognized the elastic fiber systems as a key in studying the architectural structure of the human lung. These investigators along with others (5–8, 12, 13) have observed that the transformation of the lung from a glandular to a vascular organ begins at about four and one-half to five months of fetal life and that growth is incomplete at birth.

Willson (34) concluded that the alveoli at birth are larger than those in the adult. Had he employed the elastic fiber system in his studies, he probably would not have come to this conclusion. He did not recognize the small rudimentary nature of the alveoli in the infant lungs and considered the large channels as definitive alveoli. Hartroft and Macklin (35) have made measurements of the size of alveoli in the adult lung. They have found them to be from 100 to 150μ in diameter. Although the postnatal growth of the lung is not completely understood, this investigation and those of Engel (14) suggest strongly that after three years of age the lung grows by lengthening and increase in size of the respiratory lobule composed of the respiratory bronchiole, alveolar ducts, sacculi, and alveoli. This structural unit is that observed by Grethmann (30).

The development of the elastic fibers in the lung of man has been well documented since Linser (17) made his observations. Setala (26) and Goldbach (28) have reviewed the literature and made pertinent observations on the time of appearance of elastic fibers in: the pleura, the blood vessels, and the bronchi and respiratory units. All recognize the appearance of elastic fibers in the three areas of the lung by three months of fetal life. They point out that the elastic fiber systems are incompletely developed at birth particularly in the walls of the respiratory units, i.e., the alveolar ducts, sacculi, and alveoli. Although in the present investigation the number of pre- and postnatal specimens may be considered to be limited, our observations agree with those cited above. Also, recognizing the capriciousness of the elastic fiber stain, it is probably still significant that the elastic fibers in the walls of the alveolar ducts and alveoli of the postnatal specimens are confined to areas around the mouths of the alveoli. The absence, or the presence of only a small amount, of elastic and connective tissue fibers in the walls of these structures permits opportunity for their growth and expansion during the postnatal period of development. The intense deposition of elastic fibers in the walls of the alveoli of the lungs in the young adult of 18 years and in the 27-year-old subject can be considered to represent completion of lung growth. The findings in the lungs of these subjects with respect to the elastic fibers are similar to those made by Orsós (21) fifty years ago. This writer describes the three elastic fiber systems in the lung of man: (*a*) pleura and interlobular connective tissue; (*b*) blood vessels, and (*c*) bronchi and respiratory portions of the bronchial tree. Miller's studies (22) agree with those of Orsós. W. S. Miller's observations (3) on the elastic fiber system in the lung were more or less similar to those of the above writers.

Detailed studies of the alveolar walls in the lungs of man have been made by the electron-microscope since Low (4) made his original observations with this instrument. Essentially all describe and illustrate beautifully a thin cytoplasmic membrane covering the capillaries in the walls of the alveoli. However, the origin of the cells whose cytoplasm provides this covering still is not settled. While Low (4) and others consider them to be endodermal in origin, Policard and his associates (36, 37) and others consider them to have all the cytologic and functional characteristics of a mesenchymal cell. The steady disappearance of the epithelial cells which once out-

lined the primitive passages in the parenchymal part of the human lung as it changes from a glandular to a vascular organ and their apparent lack of importance in the development of the alveoli in man suggest that these cells are replaced by others of connective tissue origin. Observations made on this series of lungs concerning the development of the pulmonary capillaries and the fate of the epithelial cells in the alveolar walls will be the subject of separate reports. From a purely histologic standpoint our observations would agree with those of Policard and associates (36, 37) who have beautifully illustrated and documented their observations with electron-microscopic procedures.

Summary

The bronchial system of the lung is established during the first five months of gestation. During this period the lung has the appearance of a glandular organ. After this time the parenchymal part of the lung differentiates and becomes converted into a highly vascular organ.

Three elastic fiber systems are present and develop independently in the lung. All begin at about three months of gestation. They are the elastic fiber systems of: (*a*) the pleura intersegmental and interlobular connective tissue; (*b*) the blood vascular system, and (*c*) the bronchi and respiratory units. These are all incomplete at the time of birth and continue to develop postnatally up to the young adult period. Some communication of these three systems is present in the adult lung. The key to the determination of the lung architecture is the elastic fiber system of the lung. The use of the elastic fiber system is essential in determining the stages in development of the respiratory unit or lobule which is composed of the terminal bronchiole, respiratory bronchiole, alveolar ducts, sacculi, and alveoli.

Although the lung becomes highly vascularized during the prenatal period sufficient to perform its respiratory function and sustain life, it is structurally not a miniature of the lung in adult man. In the premature infant the respiratory spaces are simple channels composed of vascularized walls without, or with only rudimentary, alveoli. At birth the alveoli are small and incompletely developed, as is the elastic fiber system. Elastic fibers in the walls of the alveolar ducts, sacculi, and alveoli are confined essentially to areas immediately surrounding the mouths of the alveoli. This allows opportunity for the alveolar ducts and sacculi with their alveoli to grow in length and size. Only after the adolescent period do elastic fibers develop to an appreciable extent in the walls of these structures.

Although new pulmonary units may develop up to three years after birth, as Engel has shown, lung growth after this time can be accounted for essentially by the increase in length and size of the components of the pulmonary acinus composed of the respiratory bronchiole with its alveolar ducts, sacculi, and alveoli.

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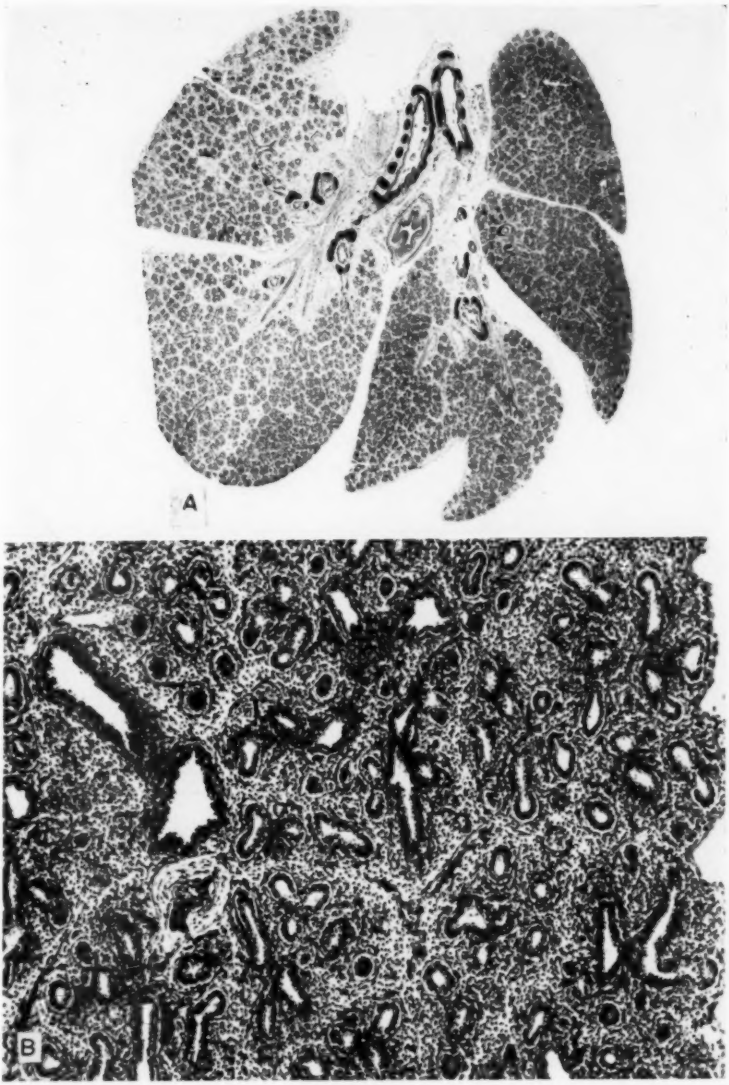

PLATE I

A. (47-736). Weight, 30 gm.; gestation, 12 weeks; stillborn. Lobulation of lung complete; cartilage in walls of main stem bronchi; lung parenchyma has glandular appearance. (Hematoxylin-eosin-azure II stain, × 13)

B. (46-116). Weight, 160 gm.; gestation, 16 weeks; stillborn. Epithelium-lined tubules are growing in a dense mass of cellular mesenchyme. (Hematoxylin-eosin-azure II stain, × 110)

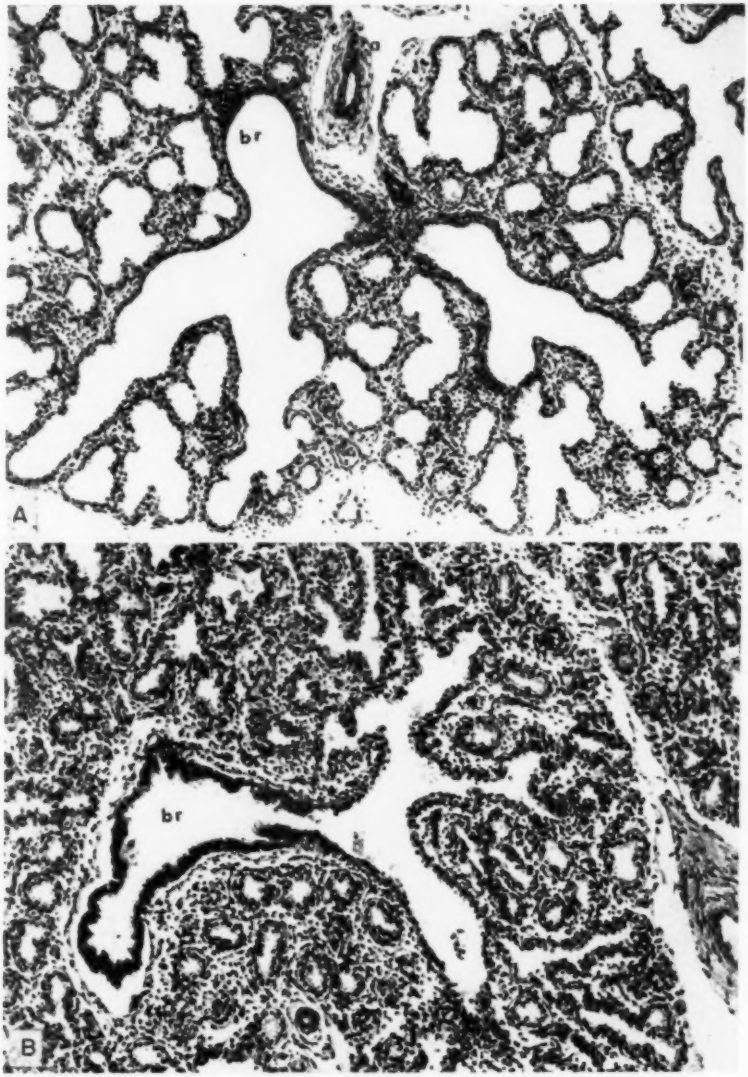

PLATE II

A. (51-416). Weight, 350 gm.; gestation 20 weeks; breathed 54 minutes. Lung expanded with fixative. The respiratory units are represented by branching epithelium-lined tubules leading from a bronchus (br.) with its accompanying artery (a). (Hematoxylin-eosin-azure II stain, × 135)

B. (48-572). Weight, 500 gm.; gestation 25 weeks; breathed 15 minutes. Differentiation of bronchial from respiratory portion of lung. Bronchial lining cells (br) stain deeply. Marked proliferation of mesenchymal elements and epithelium-lined tubules. Beginning loss of glandular appearance. (Hematoxylin-eosin-azure II stain, × 160)

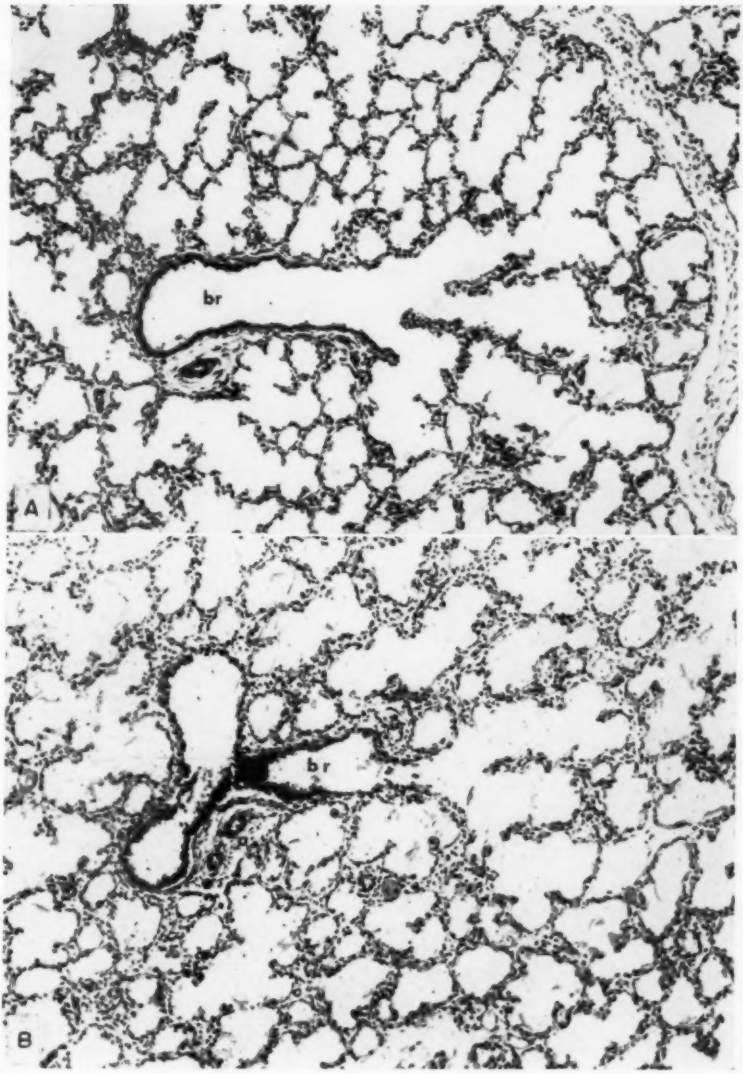

PLATE III

A. (51-417). Weight, 700 gm.; gestation 26 weeks; breathed 41 minutes. Lung expanded with fixative. Terminal bronchiole (br) with several branching channels without alveoli. Glandular appearance of lung absent. Alveoli represented as shallow outpouchings on channel walls. (Hematoxylin-eosin-azure II stain, × 135)

B. (51-380). Weight, 930 gm.; gestation 28 weeks; breathed one hour. Lung expanded with fixative. Terminal bronchiole (br) with accompanying arteriole (a). Respiratory spaces represented as large irregular channels without alveoli. Vascular development more pronounced. (Hematoxylin-eosin-azure II stain, × 135)

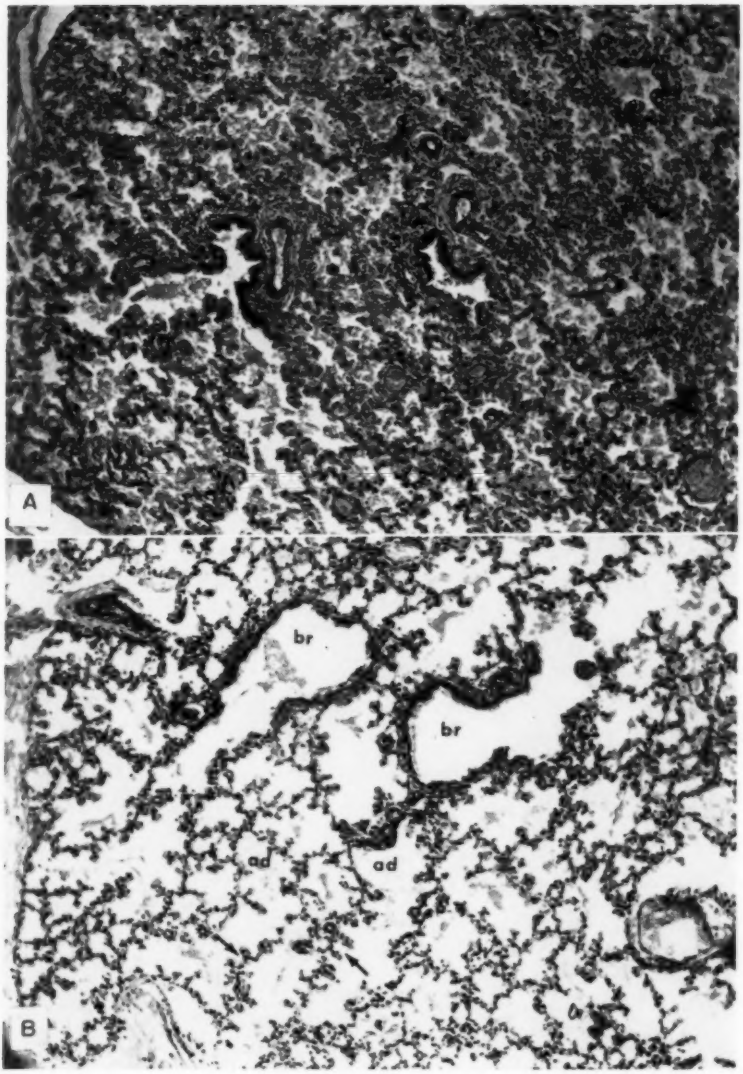

PLATE IV

A. (50-415). Weight 3,610 gm.; gestation, 38 weeks; stillborn. Lung unexpanded with fixative. Collapsed spaces contain serous exudate. Note lack of glandular appearance. Respiratory portion of lung highly vascularized. (Hematoxylin-eosin-azure II stain, × 110)

B. (50-415)—same as figure *A*. Lung expanded with fixative. Long tortuous alveolar ducts with small shallow alveoli (arrows). Deeply staining epithelial cells of bronchi (br). Walls of alveolar ducts (ad) and alveoli (arrows) highly vascularized. (Hematoxylin-eosin-azure II stain, × 110)

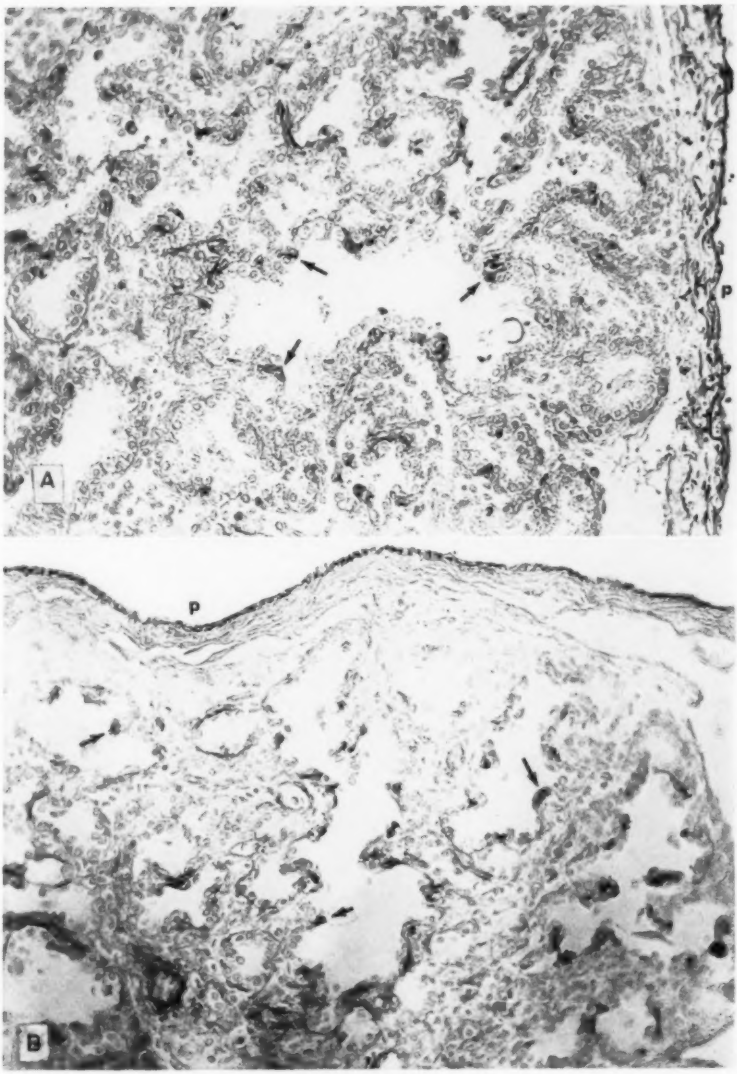

PLATE V

A. (51-416)—same as Plate II *A*. Unexpanded lungs. Deeply staining elastic fibers in pleura (p) and at points (arrows) in walls of epithelium-lined spaces. (Orcein stain for elastic fibers, × 335)

B. (51-417)—same as Plate III *A*. Lung unexpanded. Deeply staining elastic fibers in pleura (p), arteriole and at points along the thick-walled spaces (arrows). (Orcein stain for elastic fibers, × 335)

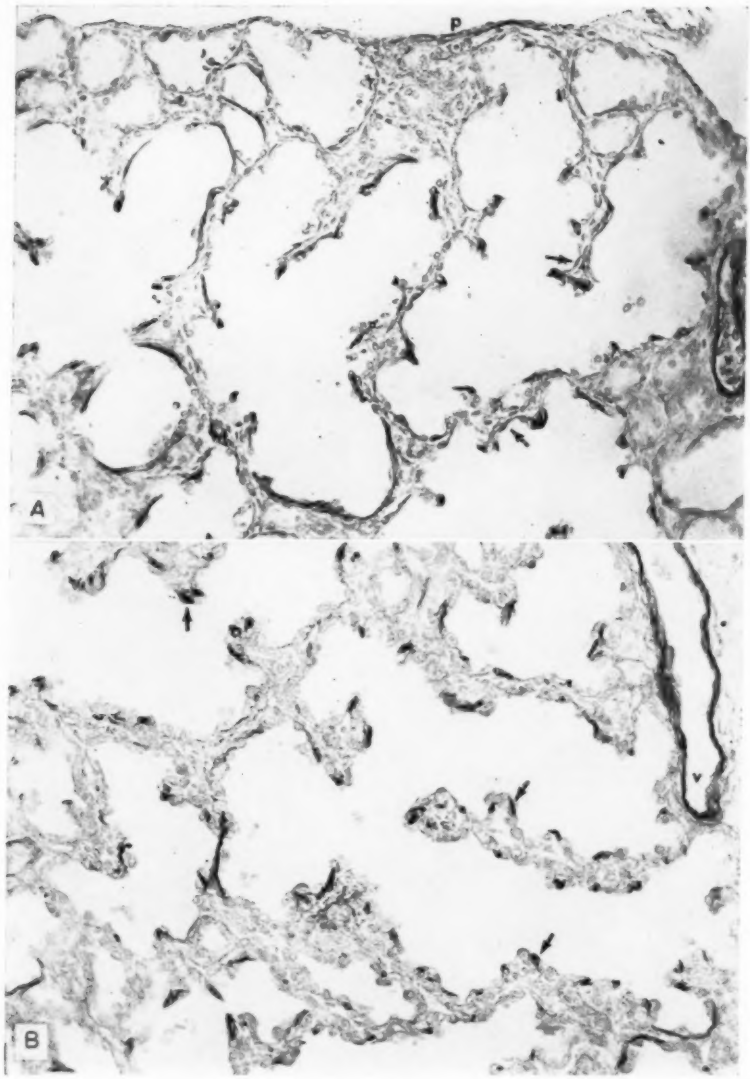

PLATE VI

A. (51-417)—same as Plate III *A*. Lung expanded with fixative. Elastic fibers in pleura (p) and vessel wall (v); cross-section of deeply staining bundles of elastic fibers at tips of projections into channels. Lung has lost its glandular appearance. Indentations (arrows) represent beginning formation of alveoli. (Orcein stain for elastic fibers, × 335)

B. (52-183). Weight, 705 gm.; gestation, 26 weeks; lived 8 days. Lung expanded with fixative. Large thick-walled spaces. Cross-section of elastic fiber bundles (arrows) on each side of channel walls stain deeply. Elastic fibers also in wall of blood vessel (v). Note loss of glandular appearance of lung. Alveoli absent. (Orcein stain for elastic fibers, × 335)

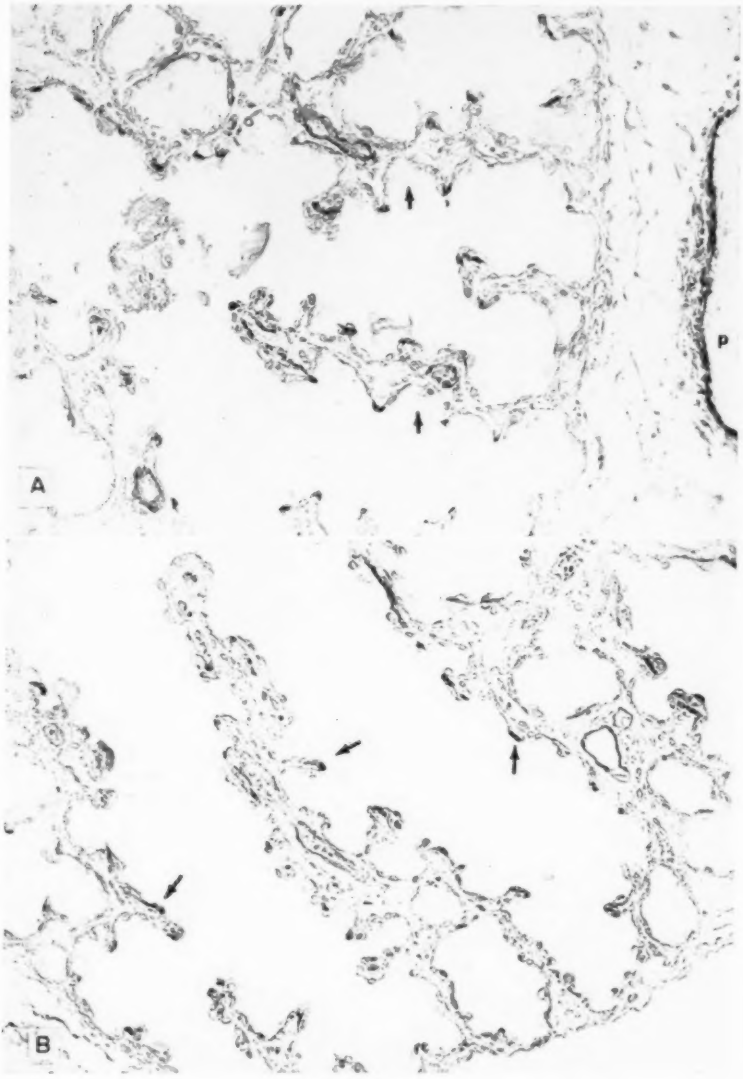

PLATE VII

A. (51-380)—same as Plate III *B*. Lung expanded with fixative. Deeply staining elastic fibers in pleura (p). Walls of air channels contain shallow alveoli (arrows). At tips of projections into spaces are cross-sections of deeply staining bundles of elastic fibers. (Orcein stain for elastic fibers, × 335)

B. (51-130). Weight, 1,350 gm.; gestation 30 weeks; stillborn. Lung expanded with fixative. Air channels large, irregular in thickness. Elastic fibers at tips of projection (arrows). Shallow outpouchings on walls represent beginning formation of alveoli. (Orcein stain for elastic fibers, × 335)

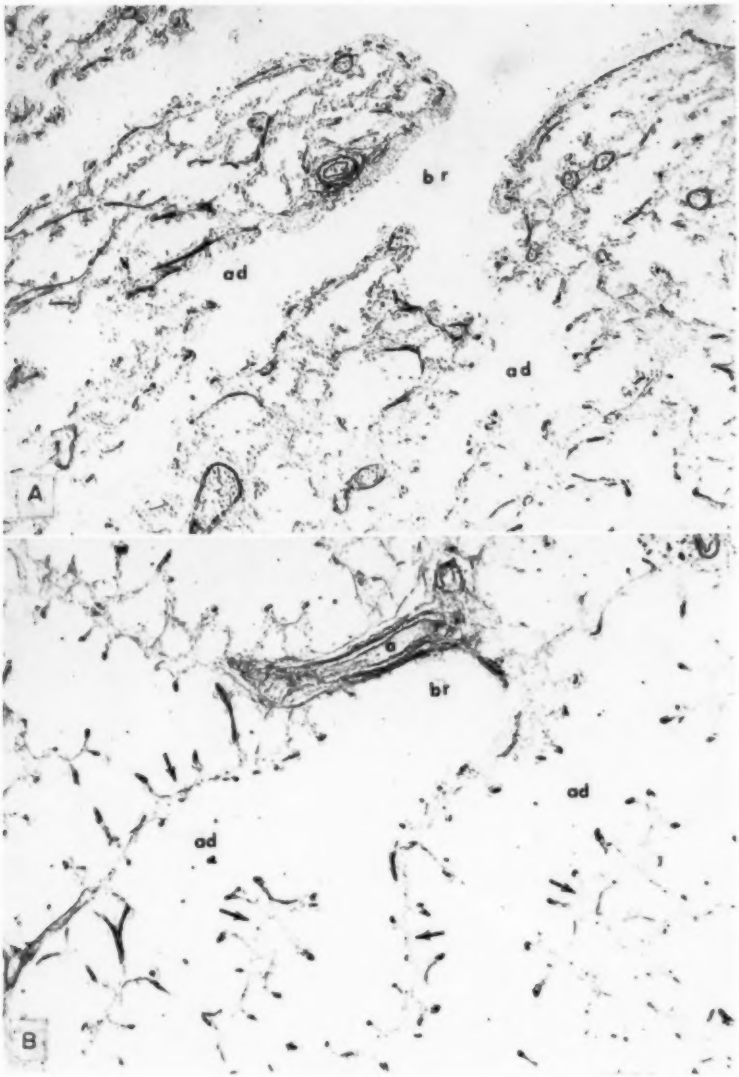

PLATE VIII

A. (50-415)—same as Plate IV *A*. Deeply staining elastic fibers in walls of bronchioles (br) and blood vessels. Along collapsed air spaces elastic fibers confined to tips of projections into spaces. (Orcein stain for elastic fibers, × 190)

B. (50-415)—same as Plate IV *B*. Lung expanded with fixative. Terminal bronchiole (br) with accompanying arteriole (a). Alveolar ducts (ad) show small alveoli (arrows) with deeply staining cross-sections of elastic fibers at tips of alveolar walls. (Orcein stain for elastic fibers, × 200)

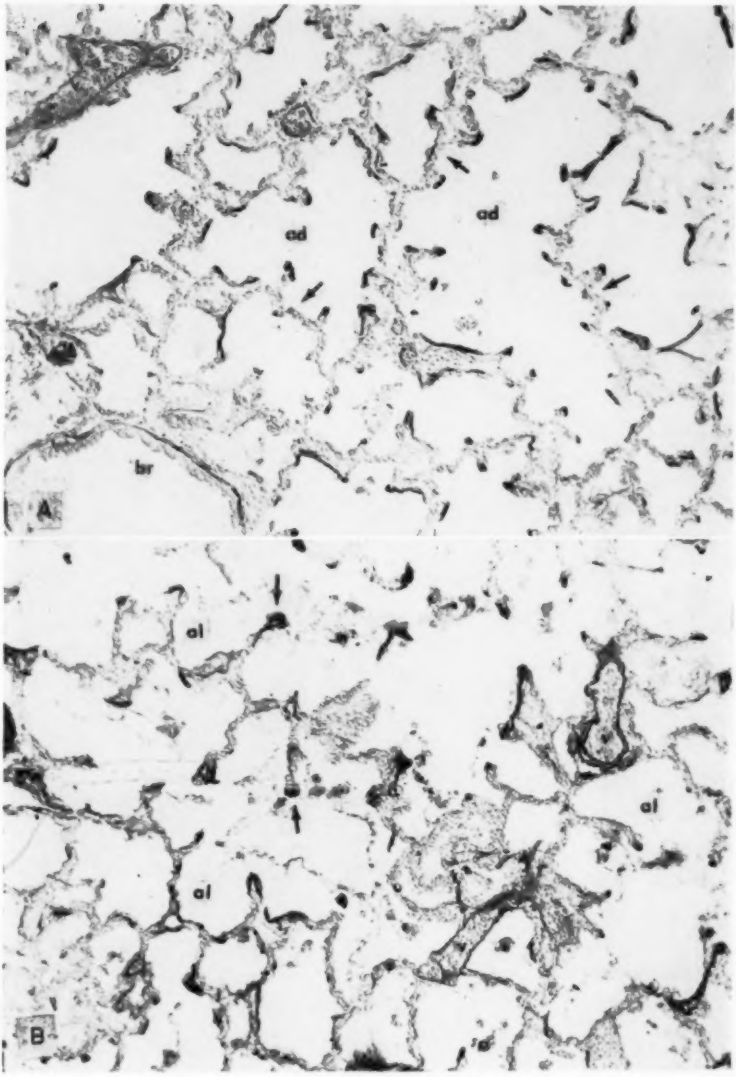

PLATE IX

A. (53-258). Infant aged 9 months. Alveolar ducts (ad) large; alveoli (arrows) small and shallow. Deeply staining bundles of elastic fibers at tips of alveolar walls. (Orcein stain for elastic fibers, × 185)

B. (10342). Child aged 5 years. Edema or serous exudate in air spaces. Alveoli (al) deeper and larger than those in figure *A*. Elastic fiber bundles show characteristic position about mouths of alveoli (arrows). (Orcein stain for elastic fibers, × 200)

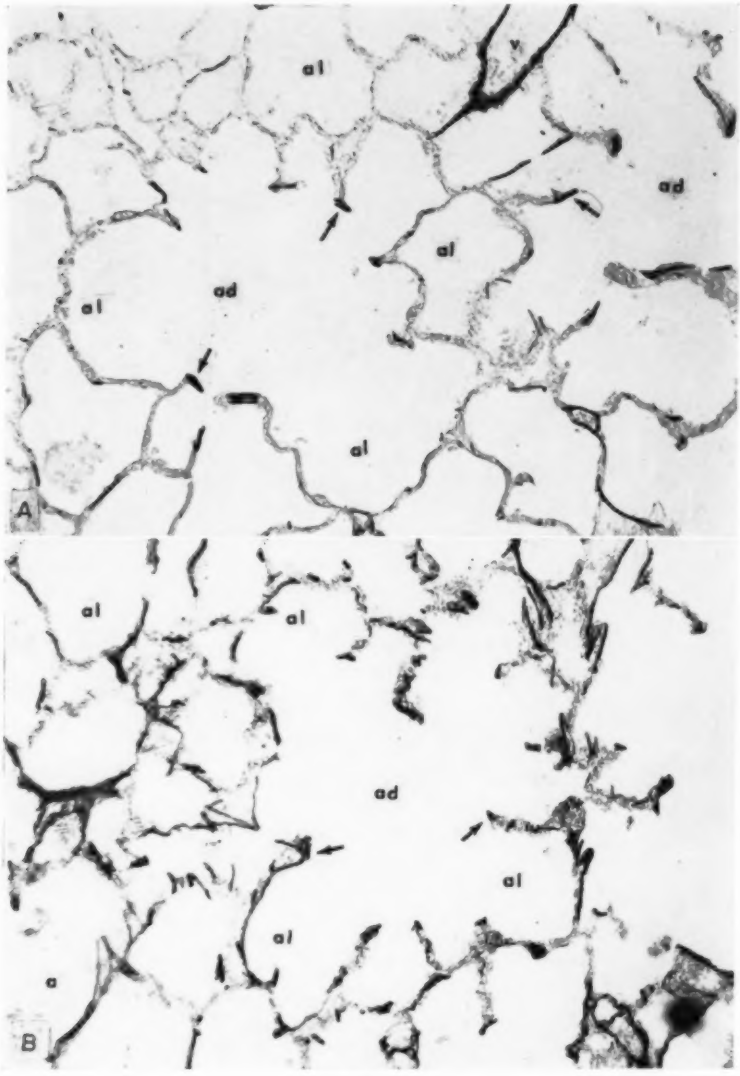

PLATE X

A. (1654). Child aged 12 years. Lung expanded with fixative. Cross-section of alveolar duct (ad) with alveoli opening into it. Deeply staining elastic fibers in walls of blood vessels (v) and cross-sections of deeply staining elastic fibers in tissue about mouths of alveoli. Segments of elastic fibers can also be seen in tissue stroma. Note increase in size of alveoli compared with those of 5-year-old child, Plate IX *B*. (Orcein stain for elastic fibers, × 180)

B. (567). Young adult aged 18 years. Lung expanded with fixative. Cross-section of alveolar duct with alveoli (al) opening into it. Note increased amount of deeply staining elastic fibers in alveolar walls compared with those shown in lung of 12-year-old patient, figure *A*. (Orcein stain for elastic fibers, × 200)

General Discussion

Dr. Eiseman: As you were talking, I thought I would like to ask all of those engaged in this work to give their opinion as to what is the best way to fix the lungs; what is the best way to stain the tissues; whether or not one should trap blood in the lungs before tying off the pulmonary artery or veins; whether one should insufflate the lungs, so that perhaps we can resolve the problem of whether fixation or staining may cause some of the overdistension that some of us amateurs occasionally call emphysema.

Dr. K. H. McLean (Melbourne, Australia): Dr. Loosli has presented a solid factual record of the development of pulmonary elastic tissue from the fetus to the adult. Having no queries about his observations, I trust that he will excuse me if I attempt to correlate his observations with some points about elastic tissue in the emphysematous lung.

It has just been demonstrated that the rate of development of elastic tissue increases greatly after birth and that new tissue may continue to form up to some time in the second decade. What is the stimulus necessary to this new formation of elastic tissue? Pathologic evidence suggests that elastic fibers will form in connective tissue that is subject to repeated stress. This is well seen in the heart in fibro-elastosis, in small arteries in which elastic fibers form in thickened intima, and in pleural adhesions which often contain many elastic fibers.

Thus, it can be tentatively proposed that the accelerated postnatal development of elastic tissue in the normal lung parenchyma occurs as a result of transition from the mild stresses of intra-uterine breathing movements to the larger stresses of normal respiration. As a corollary of this proposition, the stresses existing in the normal lung are a sufficient stimulus for the formation of elastic tissue in the lung parenchyma.

This proposition can be tested by searching for evidence of new formation of elastic tissue in lung parenchyma damaged by pathologic processes. New formation of connective tissue occurs in every inflammatory episode that does not resolve completely, but it is rarely possible in the damaged lung parenchyma to exclude the possibility that certain elements (such as elastic fibers) are *residua* of original structures. In one circumstance this proved possible: when examining the thickened walls of partially obliterated small bronchioles in emphysematous lungs, the original sub-epithelial net of elastic fibers could be recognized and was separated from the lumen by a layer of connective tissue, upon which rested the new epithelium. Below this new epithelium, and in the indubitably newly formed connective tissue, were new elastic fibers.

Unfortunately, it was not possible to obtain similar evidence of new formation of elastic tissue in more distal passages in these emphysematous lungs. Such passages bore no resemblance to normality, and indubitable evidence of new formation could not be obtained. However, the quantity of elastic tissue (and even muscle tissue) was sometimes so excessive that the only reasonable explanation appeared to be new formation of specialized tissues.

These points are made with a purpose; that is, to illustrate our ignorance of the fundamentals of tissue behavior and to suggest that emphysema is not a disease in which there is simply a loss of lung tissue, but one in which there is extensive remodeling of structure, an integral part of which is new formation of specialized tissues.

Dr. Howard Dayman (Buffalo, New York): I have three questions: (*1*) Do you believe, Dr. Loosli, that there is a change in the volume of the alveolus per se in the distensible part of the lung and, if so, what is the change? (*2*) Did you mean to imply that the development of the lung goes on until the eighteenth year of a person's life? (*3*) Finally, in your preparation, when the subject breathed eight days and there seemed to be more elastic tissue, wasn't that rather a short time for the development of elastic tissue, and does it raise the old question of whether we are dealing not with the absence of elastic tissue in the primitive fetus but with an elastic tissue which does not take the stain?

Dr. Loosli: With respect to the volume of an alveolus in relation to intrabronchial fixation, I do think the volume does become a little larger and I do think it can be actually measured, although I haven't done so. You can see from these preparations that, if you take a collapsed lung and compare it with a standard lung which is not overdistended, you can see the increased size of the individual alveolus.

I don't mean to imply that it takes eighteen years for the lung to reach maturity but, if you'll compare the size of the alveoli in the newborn with alveoli in the lung of the five-year-old, the alveoli of the five-year-old are obviously larger. They were approximately twice as large as those of the 12-year-old. The 12-year-old alveolus is about the same as that of the 18-year-old, and I am quite sure that at least up to seven years of age there is a very perceptible difference in the alveolar size when it is compared with the alveoli in an increasing age group. I can't see any development of new respiratory bronchioles, and I think that, if we could make careful measurements of the appropri-

ately distended but not overdistended alveoli in different age groups, we could almost account for the postnatal growth and the individual enlargement of the respiratory net in the individual alveolus.

Now your other question about ability to stain elastic fibers; or are they missing in the 8-day-old lung? I have used both the orcein and the Graham-Reicher stains. The orcein seems to be the best, but I have probably a dozen specimens which show this deposition of elastic fibers in the walls even though the alveoli are not patent. I assume the stretch phenomenon occurs when they are so obviously present.

Dr. Eiseman: Dr. Loosli, how much difference can you get in the size of the alveolus by different methods of fixation? In other words, if you fixed lungs in different ways, would the alveoli be the same size?

Dr. Loosli: If you keep the size of expansion in relation to the chest cavity constant (all of these lungs were fixed in relation to the size of the chest cavity), whether you fix intravenously or intrabronchially, the size of the alveoli is essentially the same, although the lungs have a little different configuration.

Dr. Eiseman: The reason I belabor it, of course, is that this is one of the parameters for determining emphysema, and it seems frequently to be a poorly controlled one.

Dr. Loosli: I am sure we don't appreciate the ability of the lung to expand when under pressure by air or by fluid. I recall experiments by Dr. Adams in which he removed all but one lobe of the lung of dogs; the remaining lobe hypertrophied and enlarged enough to occupy the entire thorax; if you examine them histologically the alveoli are tremendous, wide, and stretched, but you can't interpret this enlargement as emphysema. The lung has a tremendous ability to expand under pressure.

Dr. Dayman: Is the alveolus the distending unit or is it the alveolar duct?

Dr. Loosli: I would say that proportionately it is probably more the alveolar duct than the alveolus.

Dr. Edward Radford (Newark, Delaware): It would help a great deal if the anatomists would explain explicitly how the fixation was done, for how long, in particular. For example, Macklin and Hertog found that they had to fix *in situ* for two weeks and even then they were not satisfied that the dimensions of the thoracic chamber had maintained themselves. The diaphragm tends to move up after death, and the size of these structures at this crucial point depends upon fixation techniques.

Dr. W. A. Briscoe (New York, New York): There has been some discussion during the last few minutes about whether the lungs are simply increasing in degree of inflation after the age of five or whether they actually continue to grow or make new tissue. I was wondering whether this could be tackled by considering the weight of the lung at different ages, and whether we have reasonable information concerning what age the lung ceases to increase in weight.

Dr. Eiseman: Do you mean in density?

Dr. Briscoe: No, I mean in actual mass of lung tissue. The brain, for example, stops increasing in weight or increases only very slowly after the age of three to five years. It has gone through most of its weight increase comparatively early in childhood, and I was wondering whether the lung was the same.

Dr. Loosli: All of the tissues I presented were fixed primarily to bring out histologic detail and, therefore, they were in the fixative only six to twelve hours before they were sectioned. I am aware of Dr. Macklin's work on alveolar size, but we were anxious to get the maximum of histologic detail and fixed the tissues only for that short length of time. All were fixed intrabronchially with Zenker's solution and stained respectively with Zahn or elastic fiber stain or simple hematoxylin and eosin for cell detail. I know nothing about dry weight of lung, but at different age groups it may be noted that the wall becomes progressively less cellular in terms of cells that can be identified. I'm not sure that you would get an idea of growth of the lung by weight itself because the alveolar walls become thinner; the weight may not change, but the spaces may.

Dr. Donald Miller (Burlington, Vermont): Your very interesting paper carried us up to age eighteen, and I wonder if that remarkable study that you did on the 18-year-old boy has been used in anyone of an older age, quite apart from the consideration of whether or not he had emphysema, and what it showed.

Dr. Loosli: I have an equally well-fixed specimen from an officer who blew his brains out and bled considerably into his lung. The general histologic detail is the same. The alveoli look the same size, but I think the elastic fiber system is even more prevalent in the 27-year-old than it is in the 18-year-old. I haven't gone beyond that.

Dr. Philip Pratt (Columbus, Ohio): I would like to make one suggestion. If we want to get data, we should consider all the possible approaches. For instance, in the infant who lived eight days and had a lot of elastic tissue, the elastic tissue might be the result of his having lived; but on the other hand, he may have lived because he had elastic tissue.

Dr. William Stead (Gainesville, Florida):

Isn't there another possibility to explain the change that occurred fairly quickly? In reasoning from what we know about plastics, there could have been a realignment of the linkages of proteins; they are somewhat like plastic in this respect, namely, in the alignments of amino acids in their linkages. Isn't it possible that the stretch causes a realignment and that this may be associated with changes in the physical and chemical properties? The staining properties could change with the change in the actual fibers. As age increases, the basic fibers which have been laid down previously may change, so that in this 700-gm. fetus living for eight days it appears altogether different and *was* different physically or chemically than in the adult.

DR. LOOSLI: This is thoroughly possible and I have no theory as to what makes elastic fibers lay down in the lung as they do. Dr. Potter became so interested in this that she put a resident on the problem to make note of whether the lungs underwent some respiratory movement before the fetus succumbed. In most of these specimens, the fetus went through a respiratory movement for a few minutes up to a few days.

MICROSCOPIC ANATOMY OF THE LUNGS[1]

VERNON E. KRAHL

Introduction

In view of the specialized nature of this conference, no attempt will be made to present a complete account of the finer structure of the lung. Instead, special emphasis will be given to the more peripheral airways and to those structures which account largely for the elastic properties of the lung, for these are certain to be of frequent concern in the papers and discussions which are to follow. Since brief characterizations of the principal portions of the respiratory tree and their accompanying vessels are printed with the collected abstracts of papers presented at this meeting (1), they need not be repeated here.

Material and Methods

Pulmonary Lobules

There are structural units in the lung termed the *primary* and *secondary lobules*. When the term "lobule" is used alone, writers are frequently, but not always, referring to the larger, secondary lobules. The latter are the roughly pyramidal structures whose subpleural bases trace the characteristic polygonal markings upon the surface of the lung. Each secondary lobule is supplied by a bronchiole which enters at the apex of the pyramid and ramifies within it. The connective tissue septa which bind such lobules are continuous at the apex with the connective tissue sheath of the bronchiole and its accompanying vessels.

The primary lobule is a much smaller unit consisting of an alveolar duct, its subsequent generations of branches, plus their accompanying nerves, blood, and lymph vessels. There may be 50 or more primary lobules within a secondary lobule. The relationship between the two units of structure may be clarified by reference to figure 1. This illustrates a *terminal bronchiole* which gives rise to other bronchioles bearing alveoli and which, therefore, are termed *alveolar* or *respiratory bronchioles*. There may be from one to several generations of these, the most peripheral of which gives rise to two or more long "hallways," the *alveolar duct*. The latter are studded on all sides by alveoli. In the description given by W. S. Miller (2), the next stage would be a rotunda-like space which he termed the *atrium* (*A* in figure 1).[2] The succeeding generation is the *alveolar sac* and this, in turn, bears the terminal *alveoli*.

While the etiologic factors in pulmonary emphysema are not fully identified or understood at present, it is certain that representatives of all of the structural elements of the lung which contribute to its elastic properties are contained within secondary and primary lobules. It is likely, therefore, that the early stages in the development of pulmonary emphysema will be detected within the confines of primary or secondary lobules, or of both, and the use of these terms in their strict sense will prove most helpful.

The Study of Fresh Lung Tissue

It is generally recognized that exposure of animal tissues to fixatives, dehydrating agents, et cetera, which are commonly employed in their preparation for microscopic examination, causes certain chemical and physical alterations of the tissues, and that varying degrees of distortion may occur. The lung, perhaps more than any other organ, is subject to these unfavorable influences. Therefore, whenever possible, its tissues should be studied in fresh condition. This approach is particularly rewarding when the lungs of small laboratory mammals are used, for their small size and translucency render them suitable for observation in a small transparent chamber. When this is done, nearly all of the important constituents of the tissues commonly seen in fixed-stained preparations of lung may be observed microscopically in the fresh state (3) (figure 2) and with the assurance, especially in experimental studies, that the changes or peculiarities noted are not artefactual. Moreover, with fresh preparations, dynamic studies such as the following may be carried out: The beating of tracheobronchial cilia and the contractions of bronchial smooth muscle may be observed. In the newborn mouse, the last few generations of branches of the respiratory tree (which are always to be found still in primary atelectasis) may be made to expand from proximal to distal under the influence of subatmospheric pressure, as illustrated in figure 3. This permits the observation of the mode of branching, the number and size of each order, and an appreciation of three-dimensional relationships which may obviate the less accurate and somewhat laborious technique of plastic reconstruction (4–6). If desired, such processes may be recorded cinematographically (7). The method of observing the fresh lungs of small mammals in a transparent chamber provides a most helpful teaching aid. As an experi-

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[2] I have never observed atria in the lungs of humans or of lower mammals, but the term frequently appears in the older literature, especially. When it occurs in more recent articles, it is sometimes used erroneously to refer to alveoli or to alveolar sacs.

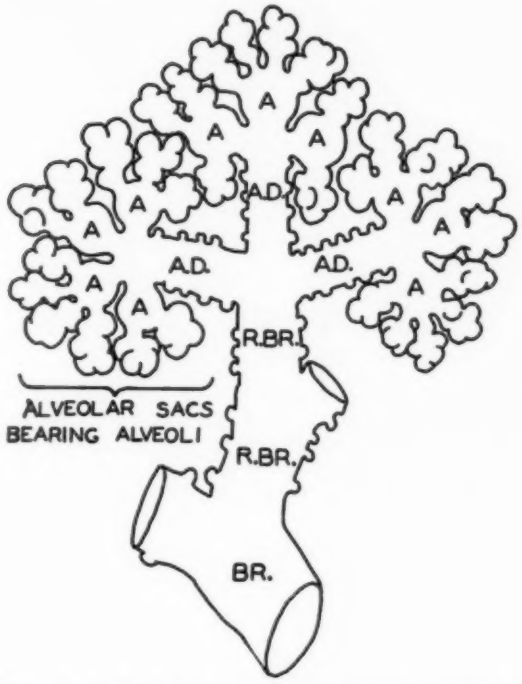

FIG. 1. Schema to show the relationships of the more peripheral branches of the respiratory tree. A—atria; A.D.—alveolar duct; *BR.*—bronchiole; R.BR.—respiratory bronchiole. Modified from Miller (2) to conform more closely to the observed contours of terminal airways of fresh lungs inflated in the transparent lung chamber (3). (*Plate used by permission of Dr. John Wagner, Editor, Bulletin of the School of Medicine, University of Maryland.*)

mental method, it permits the use of vital dyes and the direct observation of the reaction of cells and tissues to fixatives, particulate matter, noxious gases, smokes, and many other substances.

Structures Which Contribute to the Elastic Properties of the Lung

When we consider the structural elements which account for the elastic properties of the lung, its elastic fiber framework naturally presents itself as a factor of primary importance. Yet it may be shown that nearly every tissue in the lung must contribute in some degree to its total elasticity. So, in addition to an account of the elastic fiber system, brief descriptions will be given of other elements having elastic properties; namely, collagenous and reticular fibers, the smooth musculature, the blood vessels, and even the alveolar epithelium.

OBSERVATIONS

Fibrous framework of the lung: Elastic, collagenous, and reticular fibers are so intimately related that they are best discussed jointly. Although a number of the drawings and photomicrographs used here are of preparations stained selectively for elastic fibers, they will serve to illustrate collagenous fibers as well, for the latter have an arrangement and distribution quite similar to those of the elastic fibers. Figure 4 is a representation of elastic fibers of the normal human lung from the classical paper by Orsós (8). It illustrates the two principal types of elastic fibers which are classified on the basis of their relationships as *respiratory* and *circulatory fibers*. As the designation implies, the respiratory fibers are associated primarily with the walls of airways, and help to form the framework or fibrous scaffolding of all air passages. They are particularly important, together with accompanying collagenous fibers, as the elastic supports of the entrance rings of alveoli borne by respiratory bronchioles, alveolar ducts, and alveolar sacs. As Dr. Loosli has just

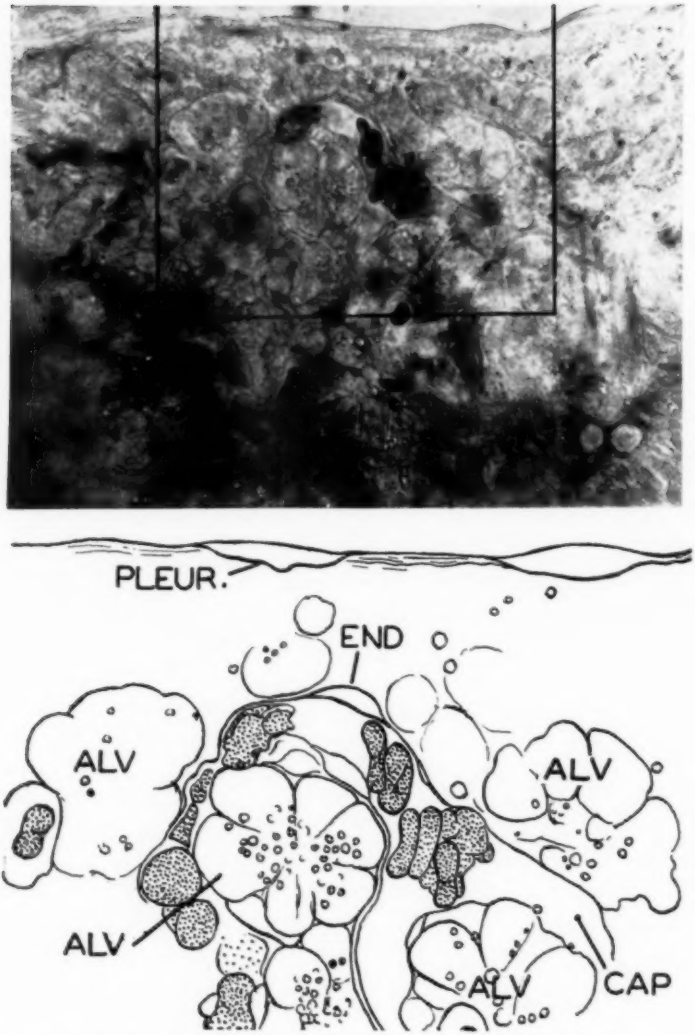

FIG. 2. (Upper). Photomicrograph of lung of newborn mouse; unfixed, unstained. Shows a small area of the persistent zone of primary atelectasis which is regularly found in the periphery of mouse lungs for several days following birth. (About 700×)

The small area outlined in the upper figure is enlarged in the accompanying labeled sketch. *ALV.*—alveolus; alveolar epithelial cell outlines are best seen at this plane of focus in the central alveolus. *CAP*—capillary; part of the network surrounding these neighboring alveoli. *END*—capillary endothelial cell nucleus. *PLEUR*—pleural mesothelial cell nucleus or margin of lung. Blood cells, both in and out of focus, are stippled. (*Plate used by permission of Dr. John Wagner, Editor, Bulletin of the School of Medicine, University of Maryland.*)

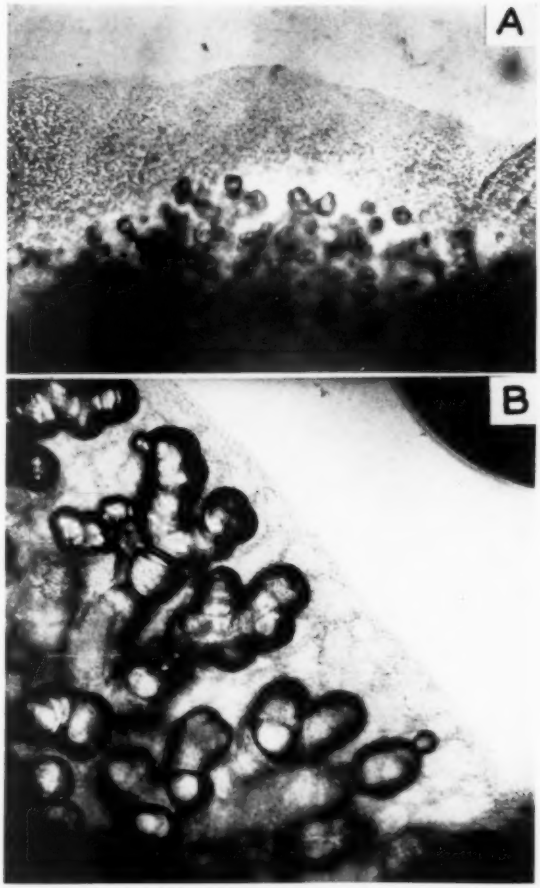

FIG. 3. *A*. Fresh lung of newborn mouse photographed in transparent chamber. Partially collapsed airways extend into the peripheral zone of primary atelectasis. (75×) *B*. Peripheral area of fresh lung after redistension of collapsed airways and inflation of more distal, previously atelectatic branches of respiratory tree. Note plump, rounded, normal contours of airways. (75×) (*Plate used by permission of Dr. John Wagner, Editor, Bulletin of the School of Medicine, University of Maryland.*)

shown in the preceding paper (9), these fibers appear in fetal lungs at about four and one-half months' gestation. They appear to serve as anchor points between which the lung continues to grow, resulting in the formation of alveoli. The circulatory fibers (*see* figure 4) form a dense plexus upon the vessels and supply filaments (not shown in the figure) which form the intercapillary elastic network.

Owing to their devious courses, elastic fibers are difficult to display over a considerable distance, even in photographs of thick (50 to 75μ) sections, for they are so numerous and intertwine in such a complex fashion that they are difficult to follow. It is helpful, therefore, to study a schema of the arrangement of a single representative fiber, as shown in figure 5, adapted from a later work of Orsós (10). Upon the outlines of two adjacent alveolar ducts, an elastic fiber is drawn which sends small projections into the margins of entrance rings of alveoli. The fiber swings around a diaphragm ring of the alveolar duct and, as it

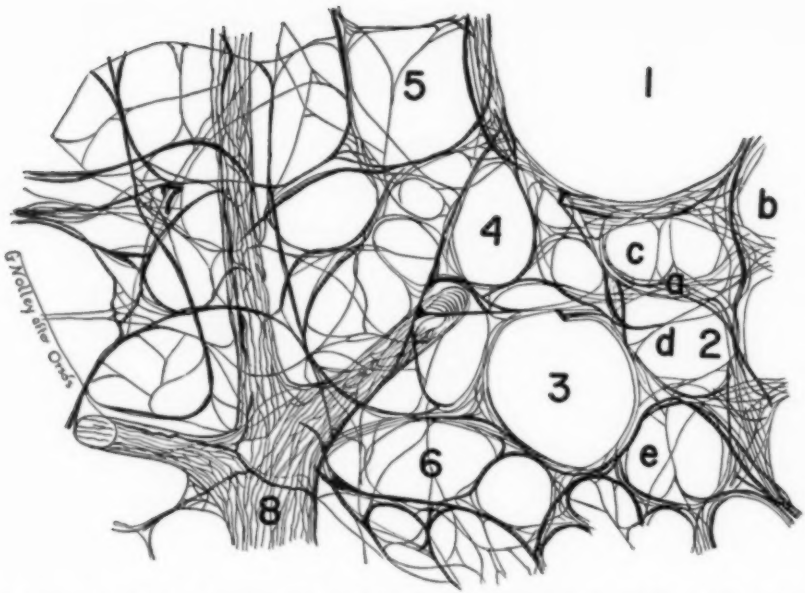

FIG. 4. Respiratory elastic framework of the normal lung: (1) lumen of bronchiole; (2) part of the wall of a respiratory bronchiole: *a*. circular fiber; *b*. longitudinal fibers, *c*, *d*, *e*, alveoli; (3) opening of an alveolar duct; (4–7) alveolar walls; (8) artery with circulatory fibers from which intercapillary fibers (not shown) are derived (after Orsós, 1936).

passes on to the next duct, provides a few fine fibers for support of an alveolar base and sends other fine filaments to an adjacent vessel and nearby alveoli. Continuing to the right, it contributes to the support of alveolar entrances in the second alveolar duct, sends filaments to another small vessel, and extends to still other neighboring structures, which are not shown. Countless fibers, wandering and interweaving in this manner, form a most astounding elastic meshwork by which all adjacent structures of the lung are intimately bound together.

In lung sections which have been stained by orcein or by Weigert's method, elastic fibers are best seen in the subpleural connective tissue, along the walls of bronchioles and vessels, and in the rounded, knoblike tips of interalveolar septa, seen in sections which pass through the entrance rings of alveoli. Subpleural fibers send projections down into the septa between subpleural alveoli. Fine fibers commonly form plexuses which support a number of adjacent alveolar septa (figure 6*B*). Perivascular elastic fibers send out fine filaments to commingle with others in the walls and bases of adjacent alveoli (figure 6*A* and *C*). Similarly, elastic fibers associated with bronchioles extend into the septa and bases of adjacent alveoli (figure 7*A* and *B*). Alveolar ducts and adjacent vessels are lashed together and supported by long, branching fibers, as shown schematically in figure 5. Essentially, then, there exists an elastic continuum in the lung, so that every airway and vessel is elastically connected to its neighboring structure. Accordingly, tensions which are developed in any part of the system are conveyed across the complex network to all other parts. As the visceral pleura follows the excursion of the thoracic wall in inspiration, therefore, a radial traction is exerted by elastic and other fibers upon vessels and airways. Local damage to the elastic framework will interrupt its continuity and prevent the uniform distribution of tractional forces, so that the walls of the smaller airways, particularly those in the immediate vicinity of the damage, are subject to a diminished radial pull upon which they depend for their patency. In pulmonary emphysema in which degradation of the fiber framework of the lung occurs, bronchioles

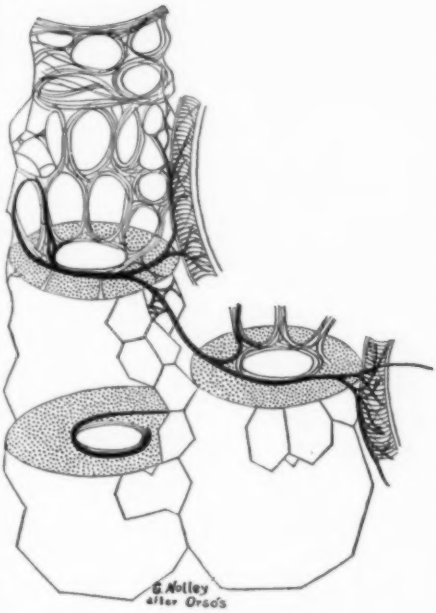

FIG. 5. Schema of framework of two adjacent alveolar ducts. Shaded discs are diaphragm rings of ducts. Openings encircled by fine fibers are alveolar entrance rings. Elastic fiber, shown in heavy black, helps bound diaphragm opening and sends sprays of filaments upon walls of neighboring arteries. For more complete description, see text (after Orsós, 1936).

under reduced traction may collapse, especially during expiration, providing a physiologic check-valve mechanism. This would foster air-trapping and further overdistension of peripheral air spaces.

Although reticular fibers do not have the same resilience as the elastic fibers, they contribute, nevertheless, to the over-all elasticity of the lung. They may be divided into more coarse, *intercapillary*, and finer *pericapillary* groups, illustrated by the schema of Orsós (10) in figure 8. These not only surround the vessels intimately, but become thoroughly entangled with the elastic fibers of both respiratory and vascular varieties, and with collagenous fibers. A clue to the importance of the reticular fibers in maintaining the integrity of the capillary networks rests in the fact that, when forces develop which overdistend peripheral air spaces, the elastic fiber scaffolding is the first to suffer. As elastic fibers are overtaxed and become broken and frayed, the capillary nets become stretched and the individual capillaries in them are attenuated. Orsós (8) has shown that, following the initial fiber damage, new, fine elastic filaments are formed which have a new and distinctive arrangement in the form of fanlike sprays spreading out across the capillary net. However, if the forces which produced the original damage persist, then these new filaments also break down and disappear. When the elastic and collagenous fibers are completely destroyed, the only remaining support is supplied by the reticular fibers. Persistent overdistension at last overcomes the reticular fiber system, whereupon the capillary beds are deprived of all support and protection from overstretching. The already attenuated vessels soon become too narrow to permit the passage of blood cells, and finally they pull apart, the torn ends retract, and the capillary bed is lost. The preceding account appears to be the sequence of events in the dissolution of interalveolar septa. As septa disappear and adjacent spaces coalesce, the large cavities characteristic of the emphysematous lung result.

Smooth musculature of the airways: Undoubtedly, the smooth muscle fibers of the respiratory tree account for a portion of the elasticity of the lung. Bronchi and bronchioles must lengthen and shorten with the phases of the respiratory cycle, as observed by Macklin (11) and many others. The smooth musculature is able to add both an active shortening and a narrowing influence to the elastic recoil of stretched respiratory elastic fibers through the peculiar arrangement of the muscle bundles. A true cross-section through a bronchus shows a discontinuous muscle layer. This is to be explained by the fact that the muscle is arranged not as a continuous sheet surrounding the airway, but as right- and left-handed spirals extending along the length of the respiratory tree as far as the terminals of the alveolar ducts. This configuration is not easily appreciated in ordinary sections of lung, but is well shown by a plastic reconstruction such as that prepared by Miller (2). A less laborious way of demonstrating the crossing spirals is illustrated by figure 9, showing the criss-crossing of muscle bands in the bronchus of a cat which was split lengthwise, pressed flat, then sectioned with the knife held parallel to the surface.

Elasticity of pulmonic blood vessels: That the pulmonary blood vessels must contribute substantially to the total elasticity of the lung is

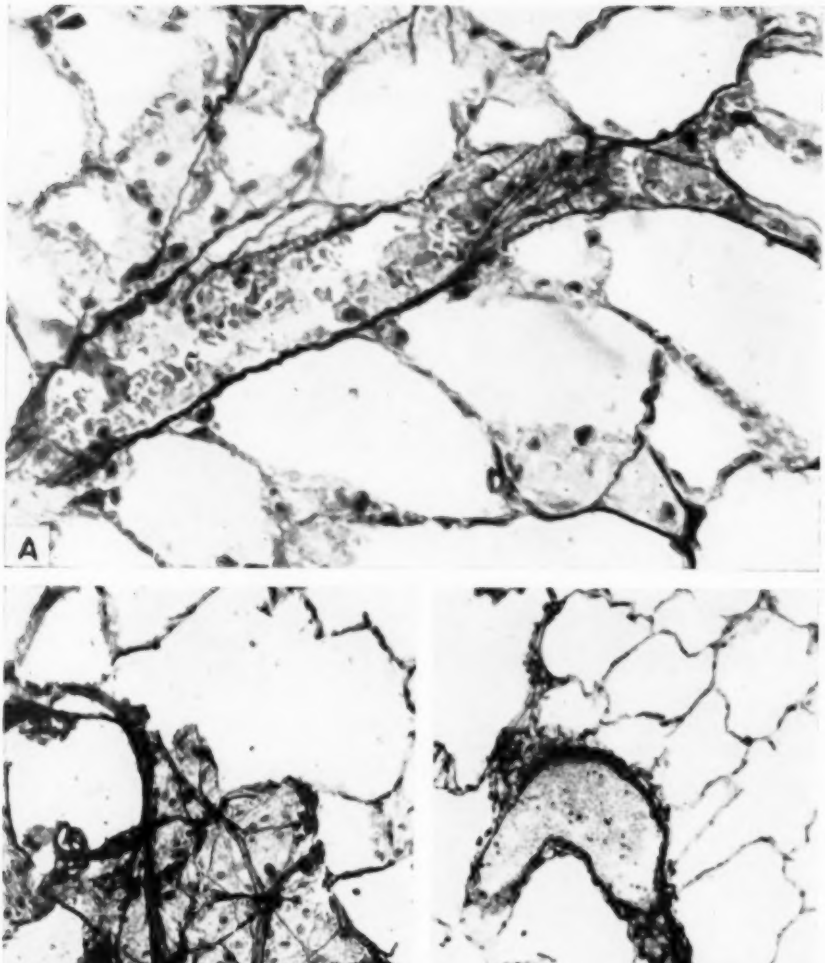

FIG. 6. Elastic fibers in the lung of the dog. (Orcein-methylene blue) *A*. Perivascular fibers, above and to the right, extend to the walls of adjacent alveoli. (400×) *B*. Stout bundles of parallel elastic fibers send out filaments which cross, join, and interweave upon several adjacent interalveolar septa. (200×) *C*. In upper left corner, elastic fibers extend from artery to wall of terminating respiratory bronchiole. At lower right, where vessel is cut tangentially, fibers wander out into interalveolar septa. (200×)

FIG. 7. Respiratory elastic fibers in the lung of the dog. (Orcein-methylene blue (430×)) *A*. Bronchiolar wall, showing intermingling of respiratory and vascular fibers on the right, and of respiratory and alveolar fibers on the left. *B*. Tangential section of a bronchiole showing longitudinal fibers of the mucosa and transverse or "circular" fibers associated with the smooth muscle. The muscle bundles (unstained) are located in the light vertical bands. Above and below, fine filaments leave the bronchiole to support adjacent alveoli.

readily appreciated in view of their rich endowment of elastic and contractile elements. The vessels accommodate not only to fluctuations in blood pressure and volume, but also, by longitudinal changes, they adapt to alterations in the over-all size of the lung which occur with the phases of respiration. The vessels, intimately connected as they are to adjacent airways through the intertwining of respiratory and vascular elastic fibers, are automatically coordinated in their adjustments with those of the bronchioles and other structures to which they lie adjacent. The larger vessels are provided with a recoil mechanism in the form of their dense vascular plexus of elastic fibers, and the smaller vessels have their inter- and pericapillary elastic plexuses. Excessive stretching is prevented in large measure by the limitations set by the elastic fibers (1.5 times their normal length).

The pulmonary capillaries deserve special mention because of their rather unique arrangements and relationships. The capillary networks of the interalveolar septa are the richest in the body—so rich, in fact, that the spaces in the meshwork are often smaller than the diameters of capillaries which surround them (figure 10). It is noteworthy that the capillary networks vary widely in their density, depending upon their location in the lung. Orsós (10) has shown that in normal adult lungs the alveoli are large, and that the capillary plexuses of interalveolar septa in the apices of the upper lobes have fewer vessels and much wider

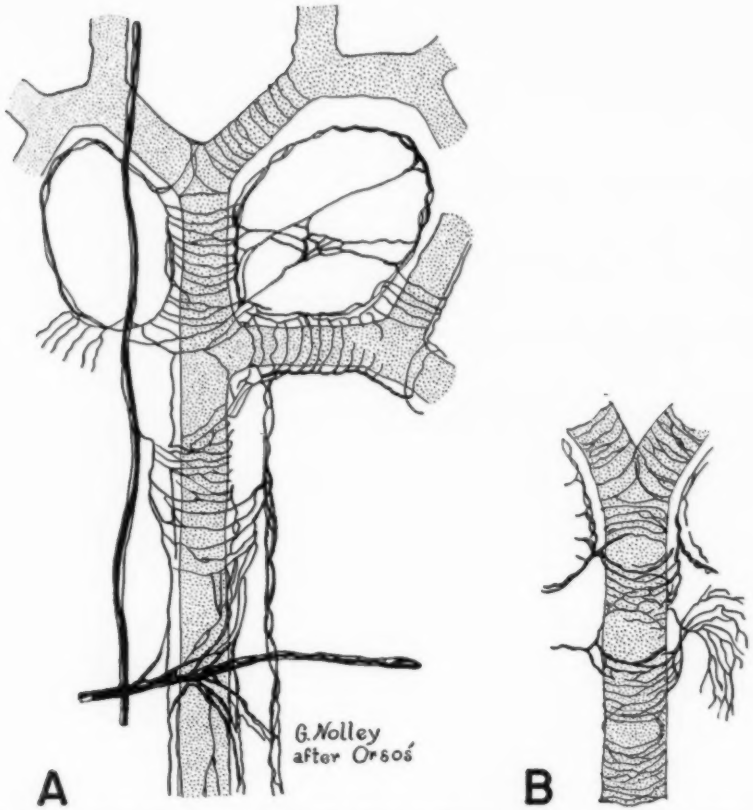

FIG. 8. *A*. Schema of relationship of reticular fibers to the capillaries. The coarse bundles of fibers running parallel to the longer vessel and forming wreathes in the capillary enclosures are intercapillary fibers. They give off fine filaments which form a loose, fibrous tube about the vessels. *B*. The adventitial reticular fibers or perivascular fibrillae, closely applied to the vascular wall and the upper part of *A* and in *B*, are seen (after Orsós, 1936).

meshes than do those of the caudal parts of the same lobes or the caudal lobes of the same lungs. This may become an important consideration in explaining sites of predilection of certain pulmonary diseases. It will have some bearing also in relation to experimental studies on pulmonary emphysema in which comparisons are made of experimental and control lungs. In such cases, the investigator must be sure that his tissue samples are taken from comparable areas of the lungs.

Whereas capillaries elsewhere in the body are usually well supported on all sides by the tissues in which they lie, those in the lung can function only if they are virtually exposed on all surfaces. The pulmonary capillaries, therefore, depend entirely for their support upon the fibrous scaffolding upon which they are suspended. As noted above, they are protected against excessive tension by all types of fibers (elastic, collagenous, and reticular), but perhaps best of all by the reticular fibers for, although capillary networks may become tensed and stretched upon the loss of elastic fibers, the vessels do not usually rupture and retract until the strength of the reticular fibers has been overcome.

Alveolar epithelium: For more than a century, the existence in the adult of a continuous alveolar

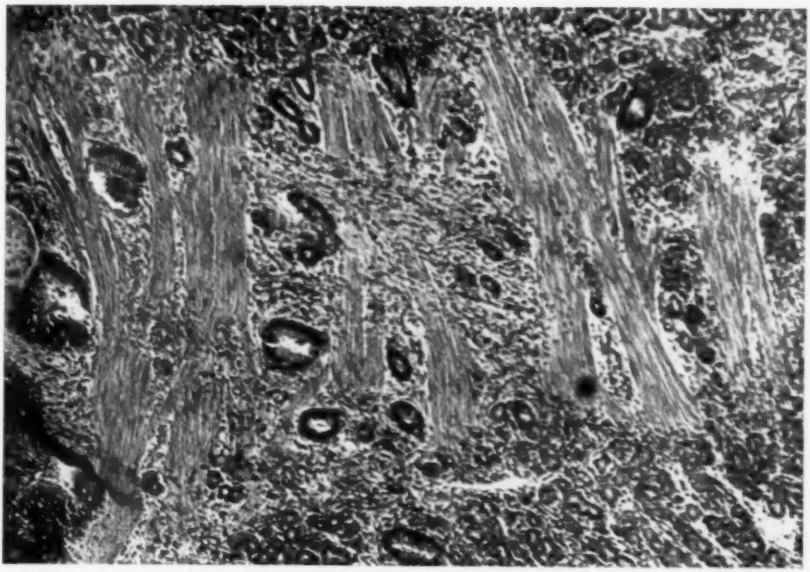

FIG. 9. Cat bronchus, slit longitudinally, opened out flat, and sectioned longitudinally to show the crossing bands of smooth muscle. Since the bronchus is taken from a collapsed lung, it is seen in its shorter, contracted condition. Accordingly, the spirals do not appear to be as steep as when the lung is partially distended or fully so, as in deep inspiration. (About 100×)

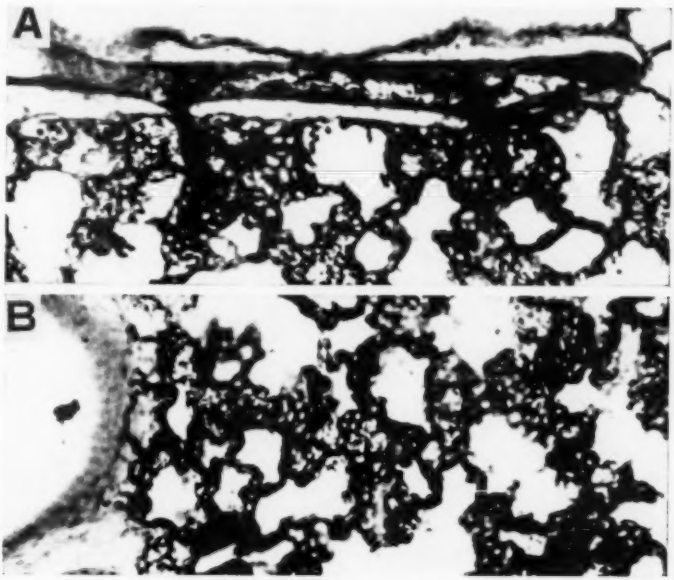

FIG. 10. Mouse lung in which capillary networks are filled with india ink which had been injected into the right ventricle of the beating heart. *A*. A branch of the pulmonary artery is seen supplying the capillary networks of interalveolar septa through short connecting vessels. (100×) *B*. Preparations similar to that in *A*. On the left, the injection has delineated an anastomosis between the bronchial circulation (bronchial artery) and the capillary network (pulmonary artery). (100×)

epithelial lining has been disputed.[3] Evidence in support of the concept of a continuous epithelium may be marshalled from various fields, including phylogeny, ontogeny, tissue culture, and pathology (3).

Ordinarily, the postnatal alveolar epithelium is so thin that it cannot be distinguished with the light microscope as a layer separate and distinct from the capillary wall against which it lies. Occasionally, poorly fixed lungs, through shrinkage, will display alveolar epithelium which has pulled away from the alveolar surface (2, 3, 16, 17). For example, Bensley and Groff (16), in a study of changes in the alveolar epithelium of the rat at birth, found that under certain conditions (moderate distension of the lungs, delayed or differential fixation, or by moderate maceration) the epithelial membrane was lifted away from the alveolar capillaries. In the newborn mouse, a cuboidal epithelium persists in the peripheral alveoli for a week or more and is gradually converted to the squamous epithelium characteristic of the adult. In some poorly fixed lungs of prenatal and neonatal mice, the writer has observed the epithelial shrinkage illustrated in figure 11. In these preparations there can be no question of the continuity of the epithelial membrane.

The most convincing proof of the continuous alveolar epithelium is given in the excellent electron micrographs published by Low (18, 19). He reports that the average thickness of the attenuated epithelium in the rabbit, guinea pig, dog, and man is 0.2μ (which is also the value for the practical limit of resolution with the light microscope). In the rat and mouse, the epithelial sheet may be thinned out to only 0.02μ. Two electron micrographs of the alveolar wall in the human are shown in figure 12. In figure 12*B*, especially, it may be seen that the attenuated alveolar epithelial cell sends a prolongation over the capillary wall, and that a tissue space (TSP) may be followed for some distance between the two. At least four barriers stand between the air in the alveolus and the blood in the capillary, namely, the capillary endothelium, its basement membrane, the basement membrane of the alveolar epithelium, and the alveolar epithelium itself.

The concept of a continuous alveolar epithelium is now gaining wide acceptance and is being presented in the latest editions of well-known textbooks of anatomy and histology (20, 21). The epithelium is of endodermal origin, being the attenuated, mature form of the original cuboidal epithelium of the peripheral airways of the fetal lung. The thicker portions of the alveolar epithelial cells which contain the nucleus are easily visible with the light microscope and, when they were earlier thought to be isolated cells, they received various designations, such as *septal cells*, *epicytes*, and "Deckzellen."

Elastic properties may be ascribed to the respiratory epithelium, for it does not become alternately taut and folded, but constantly accomodates itself to the changing dimensions of the spaces which it lines. Moreover, when it becomes detached from the wall of the air space by a transudate, as it may in certain diseases such as pneumonia or mitral heart disease (2), it contracts into the lumen of the space and may "shrink together like a flattened rubber balloon" (10). To what extent the respiratory epithelium contributes to the over-all elasticity of the lung is difficult to estimate, but it cannot be negligible. Although it is one of the sheerest membranes in the body, it is also one of the most extensive. Estimates of its total surface area vary between 75 and 100 square meters.

Mechanisms of Collateral Ventilation

If, as it appears, an important underlying factor in the etiology of pulmonary emphysema is an intermittent occlusion of bronchioles, then it is most appropriate to mention the interconnections between adjacent airways which provide a means of collateral ventilation.

Alveolar pores (pores of Kohn): Alveolar pores are small (about 10μ in diameter) round-to-oval apertures occurring in interalveolar septa. Although in our experience they are not equally numerous in all species, pores may be found in all of the common laboratory mammals and in man, provided the lungs have been suitably prepared for study. The earlier observers, in particular, considered alveolar pores to be pathologic openings, for they were frequently found in diseased lungs where, for example, fibrin threads could be seen passing through openings between adjacent alveoli. Today, the pores are generally held to be normal structures. They may be demonstrated readily in sections of lungs which have

[3] The stormy and interesting history of this controversy cannot be reviewed here. An introduction to the pertinent literature may be obtained from the literature cited in references 2, 3, 5, and 12–15.

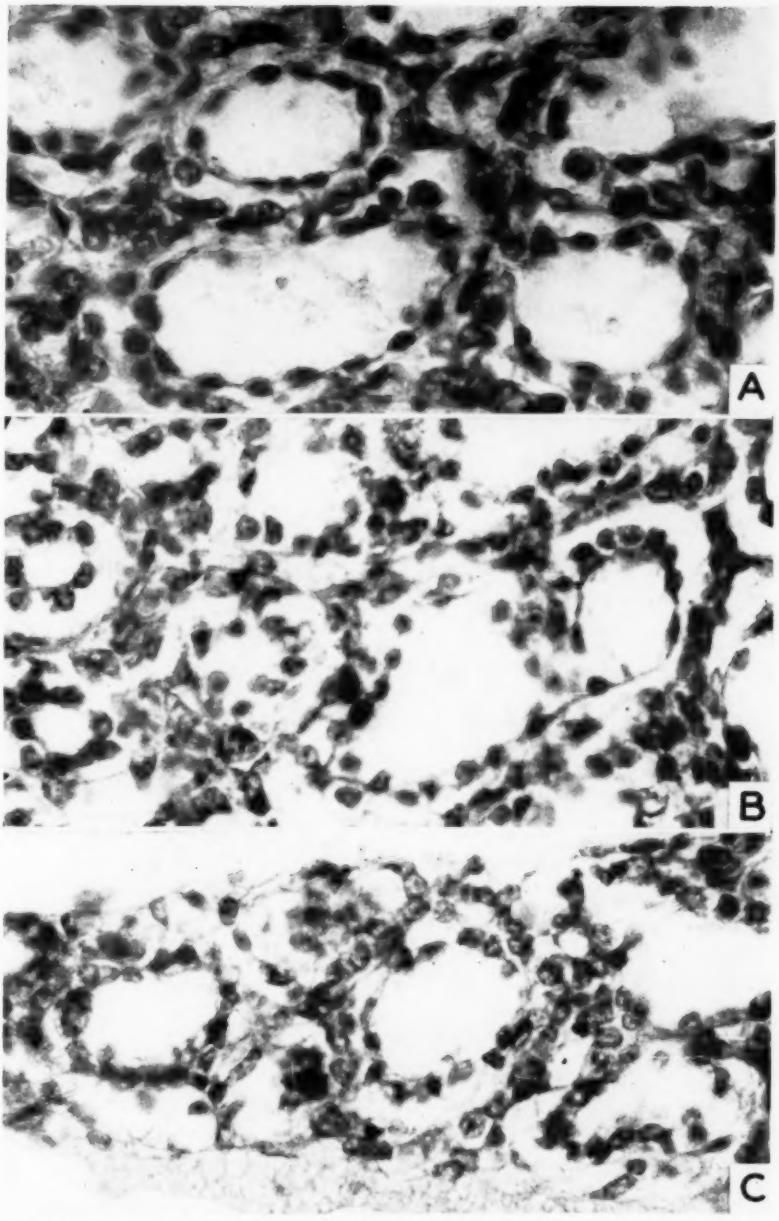

FIG. 11. Photomicrographs of mouse lungs in which severe shrinkage caused by reagents has separated the alveolar epithelial lining from the alveolar walls. *A* and *B* show alveoli in deeper areas of the lung. *C* is a section through a thin, marginal portion of the lung showing subpleural alveoli. *A*—fetus, twentieth day. Note continuity of epithelium; *B*—an adjacent section of the same lung showing a wide range in the degree of attenuation of the epithelial cells; *C*—newborn; one day old. Alveoli in peripheral areas retain a cuboidal epithelium for a week or more following birth. (10 per cent formalin, hematoxylin and eosin, 900×) (*Plate used by permission of Dr. John Wagner, Editor, Bulletin of the School of Medicine, University of Maryland.*)

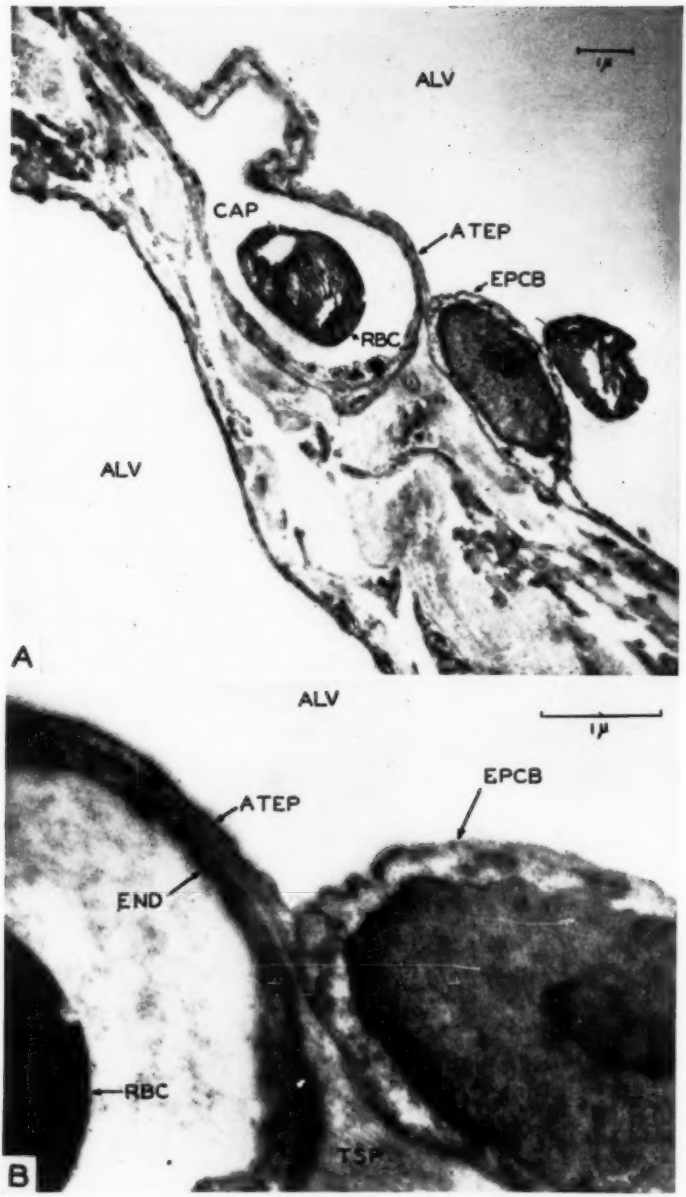

FIG. 12. Electron micrographs of alveolar wall, human lung. *A*. Epithelial cell body (EPCB) on upper surface of alveolar wall attenuates abruptly into a cytoplasmic prolongation (ATEP) which covers the underlying capillary (5,400×). *B*. The epithelial cell and capillary of *A* at higher magnification to show greater detail at the point of attenuation. The distinction between attenuated epithelium (ATEP) and capillary endothelium (END) is best seen near the epithelial cell body where the tissue space (TSP) just beneath it is prolonged for some distance between the epithelium and the capillary wall (18,750×) (Low, F. N.: Anat. Rec., 1953, *117*, 241–263. *Courtesy, Dr. Frank N. Low, Louisiana State University School of Medicine. Plate used by permission of Dr. John Wagner, Editor, Bulletin of the School of Medicine, University of Maryland.*)

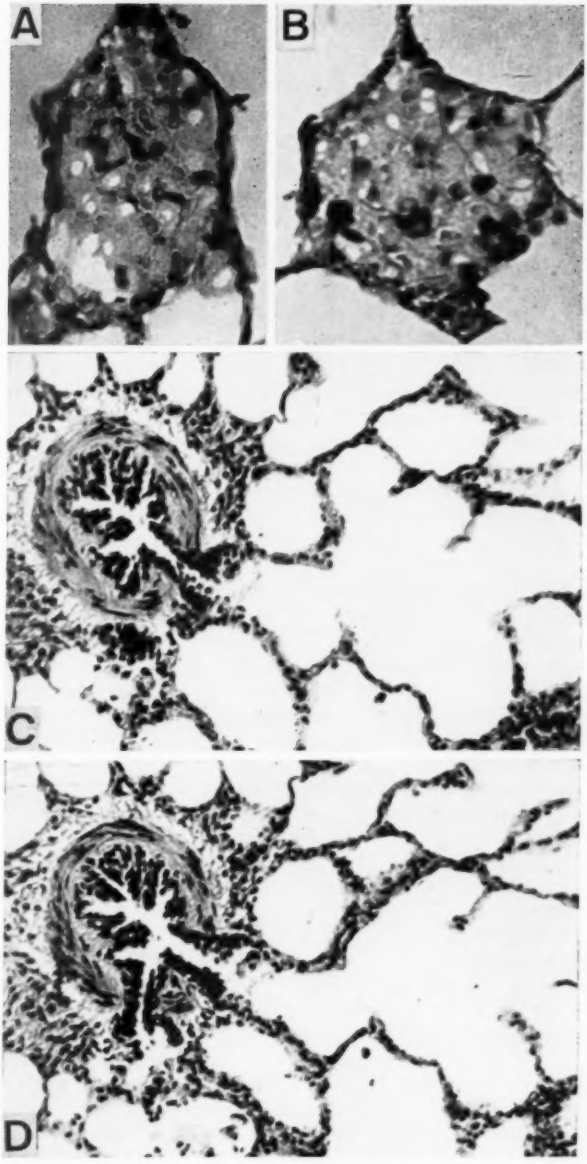

FIG. 13. Alveolar pores and bronchiolar-alveolar communications. *A* and *B*: Interalveolar septa of the dog, showing alveolar pores located in the meshes of the capillary network. In the lower part of *A* the larger openings are areas at which the septum passed out of the plane of section. Both *A* and *B* are from a lung distended to normal size by tracheal instillation of Zenker-formol fixative. (Orcein-methylene blue; *A*.—430×; *B*.—400×) *C*. and *D*: Adjacent sections of sheep lung, cut at 10μ. *C*. Small bronchiole with an epithelially lined channel communicating with an alveolus borne by an adjacent alveolar sac. *D*. The next section beyond *C* shows a second, similar communication entering an alveolus (cut tangentially) which belongs to an entirely different alveolar sac. (*C* and *D*.—200×)

been filled with colored substances (12), in thick sections (2), and most easily of all in 10μ to 20μ sections of lungs which have been distended by the fixing fluid to their normal size (22). Unlike collapsed lungs which have relaxed, sagging, and undulating interalveolar septa, distended lungs have septa which tend to be more flat and straight so that, in any given section, a considerable number of interalveolar septa are taken in the plane of section and may be inspected *en face*. Alveolar pores then appear as round or oval "windows" in the septum, occupying spaces in the capillary network (figure 13*A* and *B*). The recognition of the significance of such communications as possible pathways for the spread of fluids, cellular exudates, infecting organisms, phagocytes, and neoplastic cells, as well as their practical value in preventing lobular atelectasis in instances of bronchiolar obstruction, has occasioned the publication of works too numerous to list here. Significant contributions which may serve as an introduction to the literature are those given in references 12, 14, and 23–29.

The primary value of alveolar pores in cases of bronchial or bronchiolar obstruction in incipient or advanced cases of pulmonary emphysema would appear to lie in their ability to serve as avenues of escape for air which might otherwise be trapped in peripheral airways supplied by an intermittently blocked bronchiole. On the other hand, inflammation of pulmonary tissues, edema, collections of fluid, and the like have a tendency to block alveolar pores and thus prevent run-off of trapped air and the alleviation of local increases in intra-alveolar pressure. Medical management of pulmonary emphysema must therefore include measures which will reduce inflammation, et cetera, to a minimum.

Bronchiolar-alveolar communications: One of the most recent discoveries in lung histology is that of Lambert (30), who has reported the presence of direct communications between bronchioles and more distally located alveoli. She has found them in humans of all ages as well as in the cat and rabbit. Her study of serial sections shows that the connections may occur between a bronchiole and an alveolus belonging to a system of recurrent branches which bring that alveolus to lie alongside the bronchiole. The ventilatory value of such a by-pass in cases of bronchiolar obstruction is obvious. Lambert's findings so impressed C. C. Macklin that he arranged to demonstrate some of her original preparations at the annual meeting of the American Association of Anatomists (1957) in Baltimore (31). On this occasion, many of us became convinced of the reality of bronchiolar-alveolar communications.

It is noteworthy that Lambert prepared her lungs by tracheal instillation of the fixative and then made her studies on serial sections. The general practice of preparing lungs for histologic or pathologic study by simple immersion of the organs in the fixative no doubt explains, in large part, why such collateral channels have escaped notice until now. In recent months, the writer has found many bronchiolar-alveolar communications in the lung of the sheep. They resemble in every way the preparations of Lambert. Two adjacent 10μ sections of sheep lung are shown in figure 13*C* and *D*. A study of section *C* alone would have given no clue to the presence of a second channel nearby, while the section immediately preceding *C* would have shown no communication at all, but only a deep fold or diverticulum in the bronchiolar epithelial lining. When such folds are observed in lung sections, they are commonly considered to be simply a consequence of epithelial folding in a collapsed and perhaps contracted bronchiole. Routine distension of mammalian lungs by fixatives and a conscious search for bronchiolar-alveolar communications are almost certain to bring them to light in still other species.

Discussion

Throughout this presentation, the writer has had occasion to mention the unfavorable effects upon the lung of the various technical indignities to which we subject them as we prepare them for microscopic study. He would now like to make a strong plea for greater care and uniformity in our handling of lung tissues.

Few organs have occasioned as many vigorously disputed points regarding finer structure as have the lungs. Not a few of the differences of opinion have devolved upon differences in the handling of the lung tissues. In its remarkable adaptation to the task of gas exchange, the lung has acquired a unique, most delicate structure. As a result, it is susceptible to the unfavorable effects of fixatives, dehydrating agents, heating, cutting, et cetera, in much greater degree than most other tissues. Therefore, the microscopic appearance of lung tissue will vary greatly with the fixative used, length of fixation, method of applying the fixative (with lungs *in situ*, removed and collapsed, distended by fixative, perfused,

immersed in fixative), and many other factors (22). Whenever possible, it is well to study lungs *in vivo* or *in vitro* along with the fixed and stained preparations.

If a fixative is used, it should not be administered by vascular perfusion, for this leaves the vessels abnormally empty, somewhat collapsed or, if the perfusion pressure is excessive, overdistended. Pulmonary vessels should be ligated prior to removal of the lungs to prevent their exsanguination. A knowledge of the diameters of the conducting passages and respiratory spaces of the lung is frequently of interest in pulmonary studies. Therefore, lungs should be distended to their normal size by intratracheal or intrabronchial instillation of the fixative. When lungs are permitted to collapse and then are immersed in a fixative, not only do air spaces become far smaller than normal, but the lung or excised blocks of tissue are not fixed at a uniform rate or to the same degree. In collapsed lungs, the interalveolar septa sag and undulate so that they are seldom seen *en face* in thin sections. Accordingly, it is difficult to study the pulmonary capillary networks, elastic, collagenous, and reticular fibers, or alveolar pores. The collapse may also permit bronchiolar-alveolar communications to pass unnoticed. These are the very features of the lung which are likely to be of especial interest to those who are at work on the problems of pulmonary emphysema. In the interest, then, of better evaluation, interpretation, and correlation of investigative results emanating from widely scattered laboratories, it is highly important that the histologist, pathologist, and experimental physiologist strive for greater uniformity and care in the technical handling of lung tissues.[4]

Summary

Units of pulmonary structure, the *primary* and *secondary lobules*, are defined. The relationships of the terminal airways and some of their finer structures are shown as they appear in preparations of fresh lung tissue. The examination of freshly removed lungs by transillumination in a transparent chamber is suggested as a method which may prove useful in a number of experimental studies.

Nearly all of the structural elements of the lung possess elastic properties and contribute their share to the total elasticity of the lung. The elements considered are the elastic, collagenous, and reticular fibers, smooth musculature of the airways, the vasculature of the lung, and the alveolar epithelium.

Mechanisms of collateral ventilation in the lung, alveolar pores, and bronchiolar-alveolar communications, are described and illustrated. Their possible roles in normal and diseased lungs are considered.

A plea is made for greater uniformity in the technical handling of lung tissues by the histologist, pathologist, and experimental physiologist. The importance of redistending excised lungs to their normal dimensions by tracheal or bronchial instillation of the fixing fluid is stressed.

[4] One of the transactions of this conference was the appointment of a committee under the chairmanship of Dr. C. G. Loosli to consider and make recommendations regarding a uniform and satisfactory technique of preparing lungs for histologic examination. The report of this committee is printed in another section of this volume.

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General Discussion

Dr. Dayman: Both Dr. Loosli and Dr. Krahl anticipated my discussion, which hinges on the assertion that structure of the lung is the basis for its function. This conference should try to think of structure as it is in life, rather than in the lifeless detail presented in most of the texts on morphology. Lung tissue is subjected to stress and it exhibits strain, to employ the terms the physicist would. Stress is the force imposed; and strain, the deformation resulting. In the lung there are two systems of stress/strain. One has to do with the statics of distension and the other with the dynamics of flow. We shall deal with the static effects.

They may be observed in microscopic sections of mouse lungs, fixed *in situ* at various levels of inflation by the method of Yegian (Am. Rev. Tuberc., 1946, *46*, 109). In deflation, the alveoli are cup-shaped, somewhat like hemispheres. All structures from the intrathoracic trachea to the most peripheral alveolar sac participate in distension. Those with the most delicate walls distend the most. The ultimate distending unit is the alveolar sac. The alveolus itself opens from a cup into a saucer (Hartroft, W. S.: Am J. Path., 1945, *21*, 889), and in so doing does not share in the increment of volume; indeed, it may decrease in volume. The site of volume change is not the alveolus but the central space around which the alveoli are grouped.

This should have an important bearing on the distension of healthy and emphysematous lungs. By the term "emphysema" we refer to the anatomic form—that in which there is breakdown of the alveolar walls, causing confluence of small spaces into large spaces, even as large as an entire lobe or lung. These spaces are polyhedral but have so many facets that we may still consider them spheres. It is understandable that lung, the site of anatomic emphysema where elastic structures in large numbers have been torn from their moorings, would have to be hyperinflated to take up the slack before the forces of distension could impose stress on the remaining tissue. Such a spherical space, by means of the pressure within, would impose on the tissues about it stress equal to the greatest cross-section area times the pressure, and the tissues would resist further distension with a force equal to the greatest circumference times the tension of a unit of the circumference:

$$P\pi R^2 = T2\pi R$$
$$PR = 2T$$

This equation bears the name of Laplace, although he seems to have contributed to it only the fact that, in the distension of a bubble, surface tension of the gas/liquid interface is constant

per unit of distance. As such, the equation does not suit our purpose because elastic tension is not a constant but a variable. If we assume that the unit tension of the elastic material around the circumference varies as the first power of the radius, the effect of pressure becomes independent of the radius:

$$PR = 2KR$$
$$P = 2K$$

The volume-pressure relationship when distending a small balloon of thin, good quality rubber is shown in figure 14. Pressure mounts at first, then settles down to a lower level and usually keeps descending. The theoretic curve is dotted and we infer that the experimental curve departs from this because rubber is not perfectly elastic. In a simpler experiment one may satisfy oneself of the validity of these conclusions. Attach two balloons to a Y tube and distend them from a common source of pressure. One will distend and the other will not. Then squeeze the air from the distended balloon into the undistended one and back again. One balloon alone at a given time will retain its distension, and once distended it will remain thus until air is forced from it by some external agent. There is no inherent difference between the elastic properties of either balloon. Now test the tautness of the rubber of the distended balloon by pinching it with the thumb and finger. The state of distension is not due to failure of the rubber to exert tension at that range of stretch. The greater effect of pressure in the distended balloon has to derive from some other factor, namely, the area over which pressure is applied.

Curves of the same shape have been reported in emphysema by Christie (J. Clin. Invest., 1934, *13*, 295) and Dayman (J. Clin. Invest., 1951, *30*, 1175). Stead, Fry, and Ebert (J. Lab. & Clin. Med., 1952, *40*, 674) obtained a sigmoid curve, but the configuration differed. The salient points to be noted are the following: The volume pressure response of emphysematous lung implies that the tissues under stress are perfectly elastic. The relationship is not rectilinear and should not be expressed as compliance, at least not as a single term. The critical factor which in theory would express the amount of tissue under stress and, inversely, the degree of emphysematous change, is the *maximal static pressure* which the lung can exert. In all reports this pressure is lower than normal in anatomic emphysema, in approximately 10 cm. of water, and sometimes as low as 2 cm.

Finally, there is the enigma of the normal lung. Why does it behave as if it were not perfectly elastic? Why does pressure parallel volume? Because two variables are related does not necessarily imply cause and effect, but the structural alteration with distension provides such a capital explanation that I am persuaded that this is, indeed, the cause. As the lung distends, the tissue across alveolar domes flattens and comes more and more under direct tension. Thereby it exerts disproportionately greater counter-tension as the space further enlarges. Distension of a healthy and emphysematous lung is contrasted in figure 15.

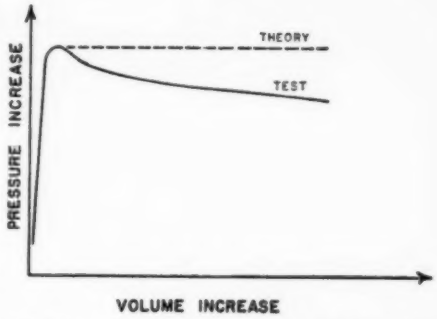

FIG. 14. From the point where a balloon is filled to take up slack, the pressure mounts to what is called "the hump." Thereafter it declines, and the decline is least when the rubber is of good quality and more nearly approaches the standards of "perfect elasticity." Since rubber never exhibits perfect qualities, there is always a difference between test and theoretic curves. When two balloons are connected to a common passage, one can be deflated on the ascending limb of the curve while the other is subjected to the same pressure on the descending limb.

DR. EISEMAN: Does this mean that all of the tensions and forces on the periphery of the alveolus are equal?

DR. DAYMAN: If we are considering spheres and emphysematous spaces in their simplest form, yes. Perhaps you will think this is oversimplified. The normal lung has, I think, special provision for distension. In simple terms, the lung tissue does not directly stretch but rather unfolds with effacement of its irregularities. The same principle is employed to impart special elastic properties to textiles in industry—to elastic garments for instance.

DR. AVERILL LIEBOW (New Haven, Connecticut): I can't comment on this, but I have a mechanical lung which I will bring this afternoon which may have some bearing on some of these questions. I am going to say something which has closer relationship to the terrestrial sphere, if I may. This is a demonstration of the pores of Kohn *in vitro* which some of you may find of interest if you are schoolteachers. Two major bronchi within

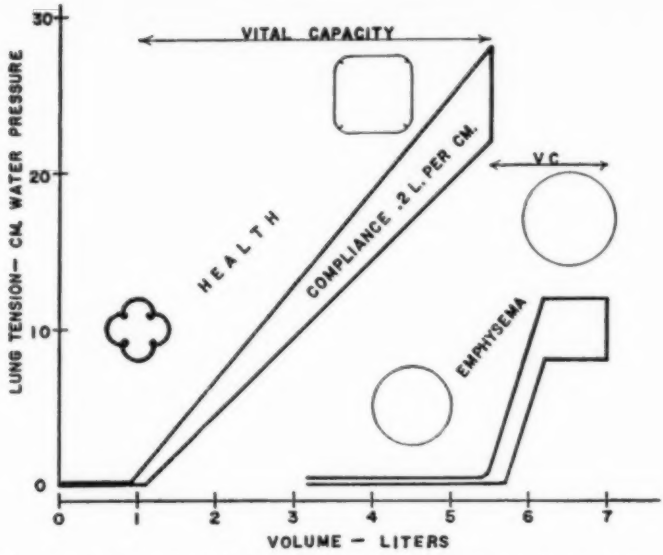

FIG. 15. Volume pressure relationship for lung in health and in advanced anatomic emphysema. This is a diagrammatic generalization of the configuration of curves and approximate quantitative values for pressure and volume. Alteration of structure, which could account for the curves, is represented over the respective inspiratory and expiratory positions. The many-faced polyhedral spaces in advanced emphysema behave as if they were spherical balloons and, in fact, the pressure volume relationship bears considerable resemblance to that of a rubber balloon.

In health, the architecture of the distensible units progressively changes. Alveoli clustered around a central space become wider and shallower and, as they do so, the elastic elements across the domes come more and more under direct tension. Meanwhile, alveolar walls are attenuated and the partition between one alveolus and its neighbor is retracted.

a single lobe of the lung of a dog are cannulated and the entire preparation is placed in a vacuum jar as indicated in the diagram (figure 16). A reasonable degree of inflation of the lobe is obtained by evacuating the jar to a pressure of, say, −5 mm. of mercury. Cigarette smoke is then gently blown into one bronchus, whereupon it escapes with great ease from the cannula in the other. When the lung is deflated by abolishing the vacuum in the jar, the lung gets smaller and smoke will no longer pass between the two bronchi. In other words, when the lung is distended, there is an increase in the size of the pores of Kohn in the lungs because the elastic traction is greater on the pores, as it is on other structures. Perhaps this is one useful application of the cigarette.

DR. EISEMAN: Dr. Liebow, can you get bronchus *B* to smoke in an emphysematous lung?

DR. LIEBOW: It would be extremely difficult to do this.

DR. RAMON LANGE (Salt Lake City, Utah): I would like to ask Dr. Dayman if he thinks the critical closing pressure concept could be applied to these spherical areas in the emphysematous lung whereas it could not be applied to the so-called accordion type of normal lung. That is, would the number of spheres be likely to exert a transmural pressure on this area and cause some spheres to dilate greatly while others would not budge at all?

DR. DAYMAN: Yes, the larger the hole in the lung, the more vulnerable it is to distension at a given pressure. That is why we have spontaneous pneumothorax in bullous emphysema.

DR. RADFORD: We have approached the problem of defining the structure of the lung in physiologic terms in an attempt to get at some of the questions or some of the factors which regulate the size of the lung. One of the characteristics of the adult lung which is very striking is the fact that it shows static hysteresis. The pressure volume curve obtained by inflating cat lungs *in vitro* in a tank was obtained with various degrees of inflation. The full volume of the cat lung is about 300 cc. If the lungs are allowed to deflate completely, they produce an S-shaped curve; if they are partially deflated, they

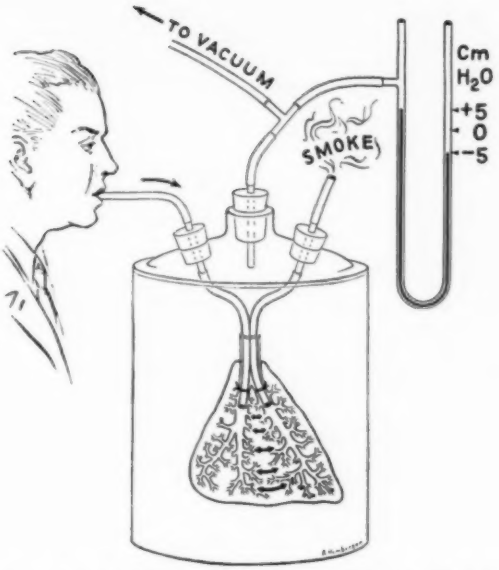

FIG. 16. Demonstration of functioning of pores of Kohn *in vitro*.

produce curves of a different type. This behavior *in vitro* is quite similar to that which we see *in vivo* with the thorax closed and also with the thorax open. You cannot collapse the lungs completely *in vivo* because of the chest wall. We are dealing here with lungs which are allowed to collapse completely.

A long time ago Von Neergaard suggested that practically all of some so-called contractive forces of the lung were due to surface tension not related strictly to its elastic properties. Cat lungs filled in a gas-free state with saline yield a curve in which there is no static hysteresis to speak of; that is, the deflation curve falls right along the filling curve. When the lungs are filled with air, however, this characteristic hysteresis is seen in the static parts; they do not change much if you hold them for long periods. In other words, you can't change the size by letting the lungs remain filled for a long time.

We attacked this problem in rat lungs by filling the lungs with various surface-acting agents to see if we could find out how much of the hysteresis was due to pure surface tension coefficient alone and how much was due to geometric changes. It took about 18 cm. of water to accomplish the inflation, with which it filled quite readily; a quite remarkably changed curve was obtained on deflation. Nothing was done to these lungs except to render them gas free, and this was done by giving the animal pure oxygen for about five minutes and then clamping the trachea. The pulmonary circulation takes up the oxygen and carbon dioxide and leaves a liver-like, gas-free lung. At the same time that we inflated these lungs we photographed the lung surface; the appearance was similar to Dr. Krahl's pictures except that this is an adult lung and we are looking directly on it. During inflation with 20 cm. of water pressure, only a small volume of lung inflated. With a pressure of 22 cm. and a little more volume, this unit which has a somewhat loculated form had now formed at least two bubbles on the surface. It took about half a day to convince myself that this was the same unit throughout all of these pictures.

At 22 cm. but with a larger volume, the lung filled slowly under this static pressure, and suddenly we had a change which made it very difficult to be sure that we were dealing with the same area. There are now a large number of small units in the rat lung which have a diameter of about 50 micra. We interpret these to be alveoli, alveolar sacs, and alveolar ducts. The lung is filling from below toward the pleura, as Dr. Dayman suggested. As the lungs deflate down to a pressure of 12 cm. of water, the configuration stays the same but, when the lungs are allowed to collapse down to 4 and 0, the size of the units does change and falls to a diameter which here becomes below the resolution

of our photomicrographic technique, i.e., below 20 micra.

We have plotted the mean area of surface unit against the air volume in the lung and, while we cannot necessarily say that this applies to all units, in some cases we can show that during the beginning of inflation we have filling of large units —presumably alveolar ducts. When we get down to a mean area of about 2,500 sq. micra or a diameter of about 50, there is a progressive smooth decrease in mean area as the lung empties. When we fill the lung with saline, it does not change the picture much. When we fill the lung with 25 per cent Tween® 20—a non-ionic water-soluble surface activator—we find that the opening pressure is about the same as before. We get a change in the opening slope of the curve, and deflation no longer shows hysteresis. If we consider the mean area of the surface units, we can show that the big units come back again as though the lung has just emptied in the same sequence as it filled. Also, the mean area of the surface units here is about 6,000 sq. micra or a mean diameter of about 80 micra as opposed to about 50 in normal lung. Tween 81 is an intermediate surface-active agent and somewhat acrophilic, but also moderately water soluble. With it you get something of an hysteresis slope; the curve is quite similar to the normal lung, i.e., sort of halfway between in all respects.

With "span 20," which is a lypophilic water- and fat-soluble surface-reactive agent, we found a completely different picture. The saline curves prior to the air curves were no different from those without any surface agent present. The opening pressure fell to about 8 cm. of water; the lung was filled at 15 instead of 24 or more, and we thus get a shifting of a deflation curve to the left as though the surface tension coefficient had fallen through the whole phase of deflation. It is important to point out that this is a very confusing collection of results, confusing for me, so don't feel too badly if it confuses you. I don't know how to interpret this yet and will welcome any suggestions that you may have, but I do want to stress one point: that, even though the lungs are fully inflated, the mean dimension of the units is quite different in the two situations, one with and one without surface activator. The difference between 50 and 80 micra is from a third to a half of the units we see.

I will close by saying that the elastic members under stress in the two situations are quite different, and the addition of the surface-active agent in this case has modified the surface action to the point where the elastic members are under stress and are different. There is different geometry of the terminal units. This would lead one to suspect that, if surface tension properties of the terminal units were modified by disease as in emphysema, it might possibly put stress on different members in that case compared to the normal state.

DR. CHARLES ODERR (New Orleans, Louisiana): With reference to Dr. Dayman's enigma of a normal lung, it might be well to remember that in the normal we are not dealing with spheres; they are actually polygons.

DR. HARRY FRITTS, JR., (New York, New York): I should like to ask Dr. Dayman a question put by Dr. Clementson. Unless I misunderstood you, you think that the Laplace equation may not apply in an emphysematous lung. This is a completely general relationship which relates the pressure inside a sphere to its elastic qualities. If you measure this pressure by having a man take breaths of decreasing depth, it might be expected that the pressure would stay constant, provided the epiglottis was open. There the tension and radius would be linearly related, but in your explanatory slide it looks as if you might have measured intrapleural pressure, and it is not at all certain that intrapleural pressure can be substituted for the pressure inside the alveolus.

DR. DAYMAN: Dr. Fritts has touched on some of the technical points which are admittedly very difficult, but it was hoped that this would provide an approach. Certainly you have no valid way of measuring the pressure, because the air is trapped in some parts but not in others, even more markedly in emphysema than in normal lungs. And I don't like to call it hysteresis when the curve becomes aberrant in inflation versus deflation, because, if we are dealing with an uneven distribution of air on inspiration and on expiration from various segments, then we really are not dealing with hysteresis in the sense of the property of elastic material.

DR. RADFORD: I would certainly agree that hysteresis as I define it is strictly phenomenologic. We make no claim that the elastic members are undergoing hysteresis. In fact, hysteresis certainly relates to surface qualitites of a very complex nature. If you restrict your definition, I would agree that this is not hysteresis.

DR. DAYMAN: I would like to comment on Dr. Fritts' comment. I agree wholeheartedly that the relationship of the dimensions of the small units should not be related to the pressure from the trachea to the outside of the lung.

STUDIES OF LUNG COLLAGEN AND ELASTIN[1]

JOHN A. PIERCE, JOE B. HOCOTT, AND RICHARD V. EBERT

INTRODUCTION

Collagen and elastin afford essential support for the parenchymal portions of the lungs. For this reason it seemed important to measure these substances in human lungs. Moreover, the possibility exists that the observed structural and functional changes in pulmonary emphysema might correlate in some manner with alterations in lung collagen and lung elastin.

METHODS

The right middle lobe was dissected at the time of autopsy. The middle lobe bronchus was transected proximal to its bifurcation. A minimal quantity of hilar material was retained on the specimen. The material was then stored frozen without fixation.

Homogenates were prepared of the entire sample with a high-speed homogenizer. Care was taken to avoid overheating. Measurements of collagen and elastin were carried out with the technique of Lowry, Gilligan, and Katersky (1). This consists of extraction in 0.1 Molar sodium hydroxide at room temperature. The subsequent conversion of collagen to gelatin was effected by autoclaving for six hours at 135° C. The procedure was followed except that the period of heated alkali extraction was lengthened to forty-five minutes, as suggested by Lansing and associates (2). Determinations were completed on 6 to 9 aliquots of the original homogenate except in three instances, when the entire sample was analyzed in four or five tubes. The mean standard errors were 4.2 per cent and 7.9 per cent of the measured values for collagen and elastin, respectively.

A material balance was completed on 6 of the samples. The mean recovery was 93.6 per cent of the dry weight input. Three dog aortas were analyzed to compare results with those in other laboratories. The values obtained agreed favorably with those published by Harkness and associates (3).

RESULTS

According to the method employed, collagen is that protein which is insoluble to alkali extraction at room temperature, but which is converted to gelatin by heat. Elastin is that substance which remains insoluble after an additional heated alkali extraction. Inasmuch as the procedure is a gravimetric one, it is obvious that the final residue will be contaminated with a certain amount of insoluble material. This is particularly pertinent in the present study since the lungs of the adults all contained visible carbon deposits.

Analyses have been completed on the right middle lobe of 20 subjects. Fifteen of these had no evidence of significant pulmonary disease on clinical evaluation or at autopsy. Five subjects had prominent bullous lesions at autopsy. One of these 5 had a clinical diagnosis of pulmonary emphysema. Terminally he had bronchopneumonia. His carbon dioxide combining power was 38 and 41 mEq per liter prior to death.

At autopsy, the major weight of the lungs is contributed by blood and extracellular fluid. This renders the wet or dry weight of the lungs difficult to interpret in terms of changes in the lung parenchyma. For this reason, the present data are not expressed relative to the organ weight.

The frequency distribution of dry right middle lobe collagen in grams is presented in figure 17. Three subjects represented in the extreme left-hand column were less than eight months of age; hence they would not be expected to compare equally with the other subjects, all fourteen years or older. The subjects who had evidence of emphysema do not seem to differ from the group of older subjects without this disease.

Figure 18 is a similar distribution curve for dry right middle lobe elastin in grams. This shows that the older subjects tended to have more elastin than the young subjects, with one exception. Among the older subjects there is no apparent difference between the group without lung disease and the group with emphysema.

The best separation of these data is shown in figure 19. This presents the ratio of lung collagen to elastin on a similar frequency distribution plot. Although the significance of such a ratio is obscure, it completely eliminates from consideration the size of the individual sample. Here, the young subjects are grouped about a mean ratio of 3.8, while the mean value of the older subjects without lung disease was 1.7. Again there is no difference between the two older groups.

[1] From the Department of Medicine, University of Arkansas Medical Center, Little Rock, Arkansas.

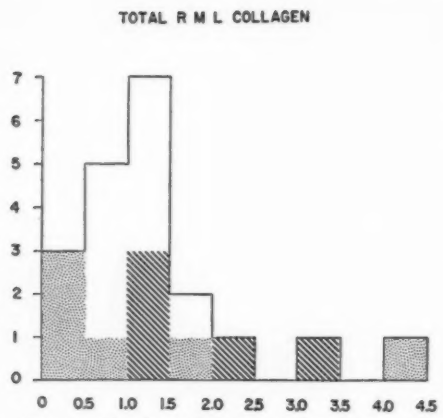

FIG. 17. Total right middle lobe collagen. The vertical axis presents the number of subjects. The horizontal axis reflects collagen in grams (dry weight). Stippled areas are young subjects without lung disease. Open areas are aged subjects without lung disease. Hatched areas are aged subjects with prominent bullous emphysema.

Analyses were carried out on a sample of hilar material (which consisted mainly of trachea) and on a sample of thickened pleura. The hilar material was not extremely different from the right middle lobe. The collagen to elastin ratio was 3.6. In contrast, the thickened pleura was almost entirely collagen, with a collagen to elastin ratio of 9.9.

DISCUSSION

Neuman and Logan (4) reported results for the collagen and elastin content of two rat lungs. Although they used a different technique, their ratio of collagen to elastin was 2.3. It is of interest that this figure falls in the range observed for humans in the present study.

The present finding of a change in the ratio of lung collagen to elastin with age is not surprising. There have been numerous reports of other changes in connective tissues with aging, particularly in the skin and in the blood vessels. Lansing and associates (5) found as much as 5 per cent of calcium in the aortic media of old subjects. This represented a fivefold or greater increase over the values obtained for young subjects. They also found differences in the amino acid composition of young and old aortic elastin.

The present elastin residues contained some visible carbon deposits. In one instance, 8 per cent of the dry residue weight was recovered by filtration of an acid hydrolysate of the elastin. This amount of correction was inadequate to elevate the ratio of lung collagen to elastin in this aged subject to levels found in the young subjects.

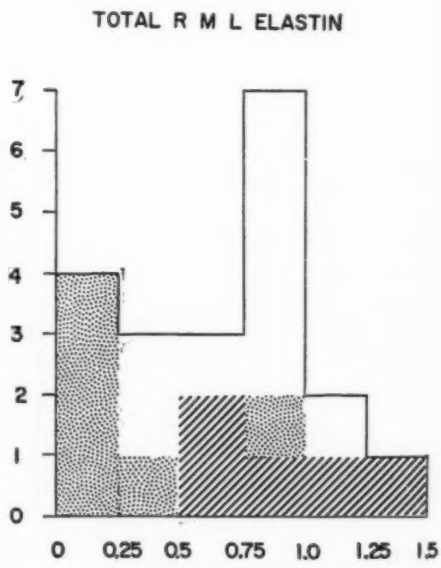

FIG. 18. Total right middle lobe elastin. The key is similar to that of figure 17 except that the horizontal axis reflects elastin in grams (dry weight).

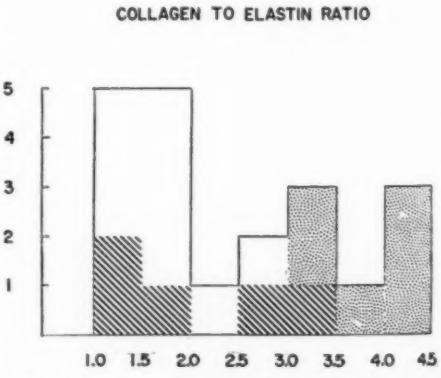

FIG. 19. Ratio of right middle lobe collagen to elastin. The vertical axis reflects the number of subjects. The horizontal axis presents the ratio.

This series is too small to warrant a final conclusion, but the finding of similar values for lung collagen and elastin in subjects with bullous lesions and in subjects of similar age without these lesions suggests that these connective tissue proteins are not primarily affected in emphysema. It is possible that some process such as inflammation might destroy the functional integrity of a fiber without attacking its entire structure. Focal damage of a connective tissue fiber would hardly be expected to result in the removal of the entire fiber because of the inherent insolubility of these proteins. The absence of a gross quantitative difference in the lung collagen and elastin of the aged groups studied in no way excludes the possibility that significant qualitative alterations of these proteins may be present.

Summary

Analyses for collagen and elastin by the alkali extraction method of Lowry, Gilligan, and Katersky were completed on the right middle lobe of 20 human subjects. There appeared to be a significant decrease in the ratio of lung collagen to

FIG. 20. Sections from an air-dried lung skeleton. This patient died of pulmonary insufficiency. The upper sections, obtained from the apex of the lung, were severely diseased. The lower sections, obtained from the lower portion of the left upper lobe, appeared relatively normal.

lung elastin with age. There was no significant difference in this ratio between aged subjects, whether pulmonary emphysema was present or not.

Addendum

It occurred to the writer that whole lungs might be extracted in a manner similar to the above described method for treating tissue homogenates. Lungs were placed in sodium hydroxide solution (0.1 M.). Once or twice daily, fresh solution was instilled into the bronchus. The extraction procedure was continued until the alkali solution remained clear (seven to fourteen days). Following additional extractions with alcohol-ether and with ether, the bronchus was connected to a compressed air source and the preparation was dried. Overdistension was avoided by the use of a respiratory valve which alternately distended the lung and permitted it to deflate at atmospheric pressure. The preparations usually dried within twelve hours. Analysis of the dried alkali-extracted lung revealed that most of its substance was collagen and elastin. Inasmuch as these are the main structural proteins of the lung, it may be considered that this preparation is a skeleton of the lung. The procedure turns the lung a white or light gray color, but does not otherwise alter the gross morphology of the lung (figure 20).

It seemed that a direct solution to the problem of connective tissue changes in emphysema might best be obtained by using these lung skeletons. Hence, the pieces of tissue shown in figure 20 were carefully cut from the lung skeleton of a person with emphysema who died of pulmonary insufficiency. These samples were selected to represent the most severely diseased and the most nearly normal parts of the upper lobe. Unfortunately, an accident in the centrifuge resulted in a loss of most of the material from the severely diseased area. Nevertheless, the ratio of collagen to elastin was 2.3 for the severely diseased area, and 1.8 for the relatively normal area. The significance of this finding will not be known until additional data have been obtained.

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General Discussion

Dr. Robert Wright (San Francisco, California): The senile changes in lungs I am sure are present as well in skin as in other organs, and I am sure that changes in collagen and elastic fibers are present. It has been shown that skin structures which have been called elastic tissue by histologic techniques are not truly elastic fibers; at least they don't act like elastic fibers as far as their tensile strength and elastic properties are concerned. Possibly a chemical or a physical approach to some of these studies might be indicated. I think Dr. Pierce's paper suggests approaches other than histologic which can be used to study senile degenerative changes of the lung.

Dr. Alfred Fishman (New York, New York): Pathologic anatomy has allowed the clinican and the physiologist to conceal, under the cloak of "emphysema," a variety of disease processes. Dr. Pierce's approach through chemistry suggests that some of these hidden entities may be uncovered by new tools. But his emphasis on the chemical aspects of the study have deprived us of the anatomic detail which is pertinent to a full appreciation of his results. I am interested in learning a little more about the nature of the "bullous emphysema" with which his subjects had been afflicted: Were the holes in the lung complications of chronic bronchitis? Were some instances attributable to primary disease of the interstitium? Did, perhaps, one subject have some hereditary disorder of connective tissue, such as Marfan's disease? Finally, were some of these instances of the group of multiple pulmonary cysts, without bronchial disease and with normal intervening lung, recently reviewed at the annual meeting of the Trudeau Society by Laurenzi from our laboratory?

I raise these questions for three reasons: (*1*) the chemical composition of the lung would be expected to differ in these different diseases as a function of the associated diseases rather than of the holes in the lung; (*2*) the holes in the lung emerge simply as a limited capacity of lung tissue to respond to a variety of stimuli rather than as an identification of any pathogenetic mechanism such as atrophy, overstretching, abiotrophy, et cetera; and (*3*) the need for clear-cut definitions and classification as a basis for communication.

With respect to the third point, I should like to call your attention to one such classification which is modified after the approach by the New York Heart Association to heart disease. Until individual diseases of the lung can be sorted more adequately on pathogenetic grounds, I believe that

we will have to rely on such descriptive categories to allow intercourse between a host of investigators with different backgrounds, orientations, and interests.

DR. PIERCE: What Dr. Fishman has described is about what has gone through our minds during the course of this study. The five people who were included as having prominent bullous lesions had just this, and in three cases only this. That is, these were people who died from other causes: one from myocardial infarction, another from acute pulmonary edema associated with arteriosclerotic heart disease. All of these people had prominent bullous lesions of the variety which we found in the patient who died of pulmonary insufficiency. The intervening lung—in fact the rest of the lung—appeared normal. Our impression is that once we soak out the exudate— the blood and other substances which tend to confuse the gross pathology of the lung—we wind up with a structure which has some rather markedly affected areas and other rather normal-appearing lung.

DR. DAVID BATES (Montreal, Canada): Now that the chemists are interested in the lung, I would very much like to draw their attention to one of the very few unanimous viewpoints between clinicians and physiologists, namely, the marked sex difference which exists in this disease. I would like to ask Dr. Pierce if anything is known about the difference of collagen and elastin ratios between the sexes and to suggest that in studying old-age pathology in the future he might think it worth while to compare men and women.

DR. PIERCE: We have no specific information on sex difference in regard to this particular problem.

DR. GILES FILLEY (Denver, Colorado): I entirely agree with Dr. Fishman that we must come to terms, but I would like to say that it's very exciting to see the possibility that by a combination of chemical and morphologic studies of elastic fibers a very important question might be answered. Is there any difference between elastic tissue which has been damaged by excessive trauma or infection, or both, and elastic tissue which suffers from some intrinsic degenerative change? The answer to this might give us a clue to the answer to one of the basic questions to be studied at this conference, namely, what is the initial insult in "pulmonary emphysema"?

DR. LIEBOW: I think, in dealing with the lung, that we are at a particular disadvantage in regard to analysis because it consists mostly of air which can be impinged upon by the addition of new substances. If something is added that does not deviate far chemically from the original structure, this may not appear in the ultimate analysis unless this difficulty is kept in mind. We have seen this recently in an attempt to analyze a disease of the lung in which protein is deposited in the alveoli. The total weight per unit volume is enormously greater, but analyses do not show striking differences from normal lung.

Second, in dealing with ratios, analyses indicate either that there is less of something, say elastin, or that there is more of something, say, for example, collagen. And this is especially true in a situation like bullous emphysema, in which most of the alveoli have disappeared and what is left is a series of bronchi and vessels without alveoli. This may not represent any fundamental change, but there is certainly a relatively higher proportion of bronchi and vessels than before. In addition to that, such a lung is also disordered in the sense that many new things appear—more muscle and more epithelium, for instance—as the lung is finally revised to yield something called emphysema.

DR. BASIL REEVE (Denver, Colorado): What relationship exists between the elastin and the collagen demonstrated histologically, measured chemically, and then studied under the electron microscope? At one time it was very difficult to differentiate between these two substances by the electron microscope. This may have changed with the new equipment, but I think that, if we are going to talk about these substances by different techniques, at least we must know what relationship they have to each other.

DR. PIERCE: Dr. Reeve, I do not believe your question can be answered because the data are not available. It should be stated, however, that in pure preparations the appearances of collagen and elastin under the electron microscope are quite different. Collagen has a characteristic periodicity of transverse striations which is not seen in elastin. In our study, it has been possible to demonstrate that lung collagen contains a large amount of hydroxyproline (similar to other collagens), and that lung elastin contains a small amount of hydroxyproline (similar to other elastins).

DR. SAMUEL BUKANTZ (Denver, Colorado): I would like to emphasize what others have said, that terminology must be specific when you get into the chemical field. I think that the methodology which is described is still pretty crude. The techniques do not have the advantage of specific hydrolysis, for example, or the hallmark of a specific amino acid which can be quantitated. Furthermore, comparisons between normal and abnormal tissues may readily be confused by the presence of contaminating substances which make comparative studies of crude extracts extremely difficult to analyze. I think we must be very careful to avoid falling into the trap of saying "collagen" or saying "elastin" when actually we are talking about an alkali-insoluble, autoclaved hydrolyzable, and then alkali-soluble material.

PULMONARY LYMPHATICS[1, 2, 3]

With Reference to Emphysema

C. E. TOBIN

Introduction

This morning I wish to speak to you about one of the most perplexing problems of human anatomy, namely, the pulmonary lymphatics.

In a request for a reprint of my paper "Human Pulmonic Lymphatics," a radiologist wrote:

> I rather hope that one comment in your article might prove erroneous. You say that it is not feasible to study the lymphatics in the normal intact chest without disturbing pulmonary function and thoracic relationships. While I admit that a study that would make this possible would be extremely difficult, I still hope that it is not impossible and might someday be pursued . . . .

I too hope that this might be pursued, but until that day the following anatomic study of the structure, together with an attempted deduction of the course of flow in the human pulmonic lymphatics, is presented to you strictly from the point of view of an anatomist.

Most of the present concepts of the pulmonic lymph flow are based on Miller's work in 1947 (1), which in summary states that: (*1*) lymphatics do not extend as far as the atria, alveolar sacs, or alveoli; (*2*) lymph flow in the peribronchial and periarterial lymphatics is in a centrifugal direction, toward the interior of the lung, where it empties into perivenous lymphatics at the level of the alveolar ducts; (*3*) only the perivenous lymphatics drain toward the hilar nodes, except for a narrow zone (2 to 3 mm.) just beneath the pleura where the valves in the lymphatics point toward the pleura. This is the only site of communication between the superficial (pleural) and deep (periarterial, peribronchial, and perivenous) lymphatics; (*4*) drainage in the pleural lymphatics is around the periphery of the lobes to the tracheobronchial nodes; and (*5*) no lymphatics are in the pulmonary ligament.

In attempting to verify Miller's concepts, the following methods of study were used which lead to the following conclusions.

Embryologically, the lymphatics invade the hilar region of the lung during the second month and by the end of the third month of gestation they have extended along the bronchi, pulmonary artery, and pulmonary veins to the pleural plexus. These findings confirm those of Kampmeier (2) and Harvey and Zimmerman (3) who had previously studied the embryology of the pulmonary lymphatics.

The normal structure, the course, the relationships, and the connections of the channels, valves, and nodes were studied from dissections and from sample and serial sections of children's and adults' lungs. The sections were stained by various dyes to bring out certain desired characteristics of their structure.

Then, in an attempt to further clarify the course and connections of the pulmonic lymphatics, solutions of india ink, vinyl acetate, or liquid latex were injected into the lymphatics. Such injections were first attempted into the cephalic and caudal ends of the thoracic duct or into the hilar lymph nodes but, in both of these cases, the position of the valves and their direction prevented the injection material from entering into the pulmonary lymphatics. Next, the pleural lymphatics and their connections with the deeper lymphatics were injected in fetal lungs (Plate I), but such injections could not be done in the normal adult lung. As shown previously by MacCallum (4), if edema or pneumonia were present in the adult lung, the pleural lymphatics (but not their connections with the deeper lymphatics) could be injected.

Since the normal microscopic studies, the dissections, and the injection studies were inconclusive, additional studies were made from sections of pathologic lungs.

Sections from lungs containing tumor cells, either primary in, or metastic to, the lung (except for helping to visualize some of the major lymphatic channels) did not help in ascertaining

[1] From the Department of Anatomy, University of Rochester Medical School, Rochester, New York.

[2] This study was aided, in part, by the Health Association of Rochester and Monroe County.

[3] In regard to this presentation, more detailed descriptions of the technical procedures used and the references to the literature may be obtained from: Tobin, C. E.: Lymphatics of the pulmonary alveoli, Anat. Rec., 1954, *120*, 625; and Human pulmonic lymphatics: An anatomic study, Anat. Rec , 1957, *127*, 611.

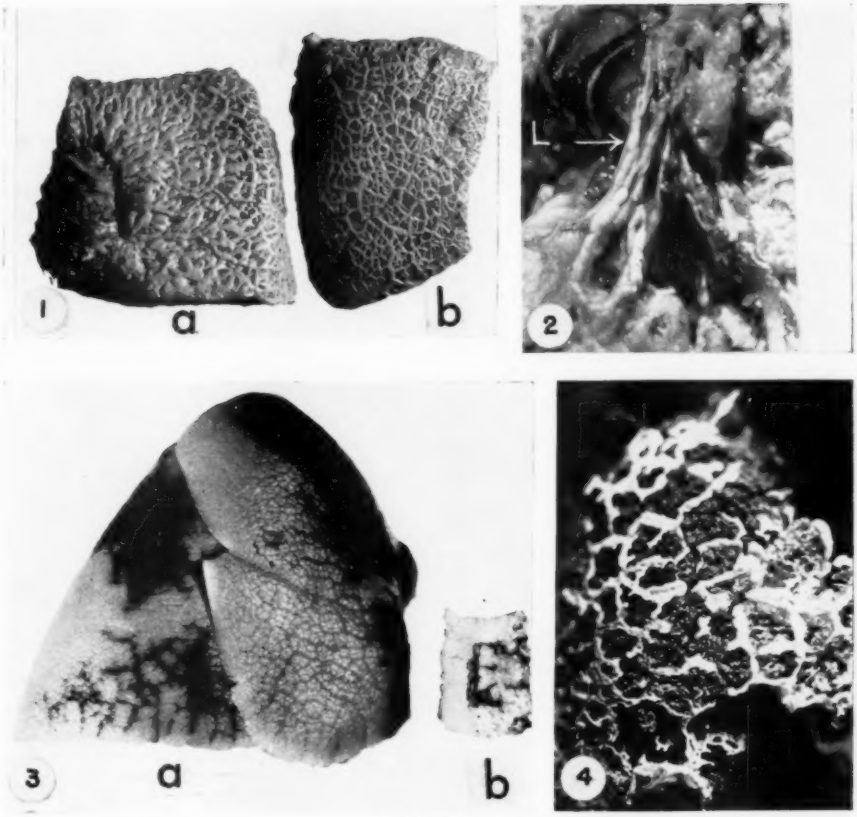


PLATE I

FIG. 1. Part of the left lung from a 6-month fetus in which the pleural lymphatics were injected with liquid latex. Note the relatively large size of the lymphatics in the cardiac area (*a*), as compared with the costal area (*b*). (× 5)

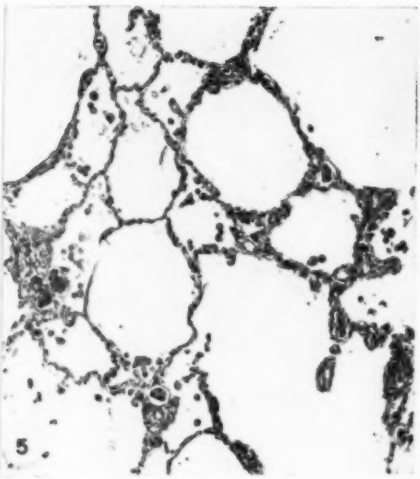
FIG. 2. A hilar lymph node (*N*) and its afferent channels (*L*) which were injected with yellow liquid latex via the pleural lymphatics in a 4-month fetus. The respiratory tissue was injected with white latex. Yellow latex was in the node; whereas the afferent lymphatics contained both yellow and white latex, resulting from perforation of superficial alveoli by the needle used to inject the pleural lymphatics, with spread of the white latex from the alveoli into the peribronchial and periarterial lymphatics. Note constrictions in the lymphatic channels which correspond to the location of the valves pointing toward the node. (× 20)

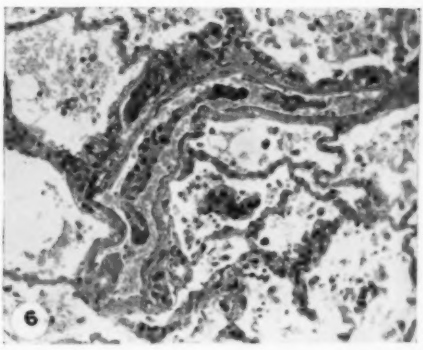
FIG. 3. Right lung of a 4-month fetus showing areas of the pleural lymphatics injected with india ink. Note in the injected areas of (*a*) the ink in the lymphatics over and around the edges of the lobules, and in (*b*) a cut surface of the lung showing injected lymphatics extending from the pleura (left) around the edges of the lobules and into the deep lymphatics (right). (×1½)

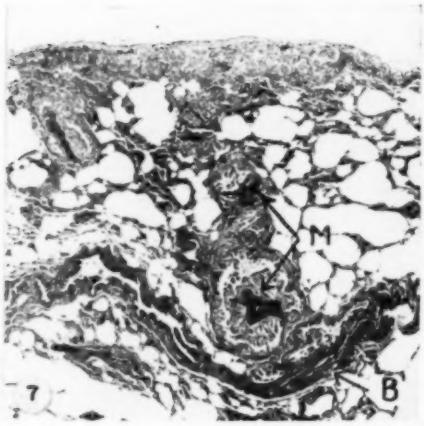
FIG. 4. Casts of the pleural lymphatics injected with white vinyl acetate from a 5-month fetus. Note the course of the lymphatic casts around the edges of the lobules. The respiratory tissue was injected with blue vinyl acetate. (× 25)

the course of lymph flow, for the intrapulmonic lymphatic spread of tumors was variable (Plate II) and did not fit any definite pattern, although 11 tissue types of tumors were studied.

More definite information of the routes of lymphatic flow in the lungs was obtained from studies of lung sections containing edema and from the lungs of animals made edematous by







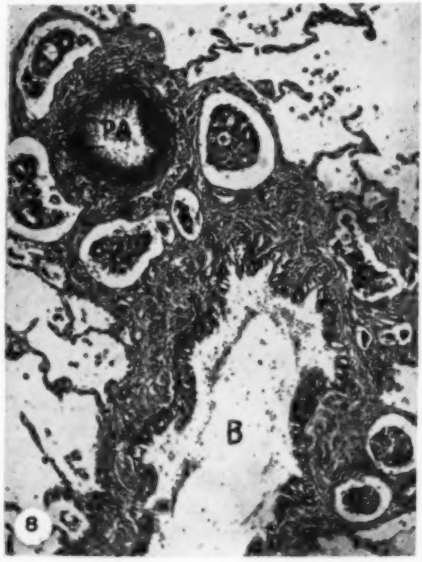


PLATE II

FIG. 5. Section through the lung of an 83-year-old male who died of metastatic cancer of the prostate. Groups of cancer cells were present in the lymphatics accompanying branches of the pulmonary artery and veins and in a vessel in an interalveolar wall (upper left). (× 100)

FIG. 6. Section through the lung of a 65-year-old female, whose death was due to cancer of the breast. Note masses of cancer cells within the lumen of the pulmonary vein, in lymphatics around the vein, and within an alveolus. (× 125)

FIG. 7. Section through the peripheral part of the lung of a 62-year-old female who died of metastatic hypernephroma. Note the dilated septal lymphatic containing clumps of metastatic cells (*M*). This lymphatic extends from around a bronchus (*B*) towards the pleura. (× 100)

FIG. 8. Section through the lung of an 80-year-old male, whose death resulted from cancer of the prostate. Note the enlarged lymphatics, containing metastatic cells, around the pulmonary artery (*PA*) and bronchus (*B*). (× 100)

the intraperitoneal injection of alpha-naphthyl thiourea, since certain lymphatics were involved sequentially and consistently.

A study was made of lungs which contained various amounts of "carbon," although it is realized that silica and other noxious materials may be present in the carbon deposits. Yet, for the sake of this presentation, it is assumed that the

inhaled carbon was at most only slightly irritating to the lung tissue. In those lungs which contained only small amounts of carbon, the carbon was found in the alveoli and in the connective tissue around the lymphatics of the respiratory bronchioles (Plate III, figure 9). In other lungs which contained larger amounts of carbon, it was also found in the connective tissue around the afferent lymphatics to lymphoid tissue located at the bifurcations of the bronchi and in the hilar nodes (Plate III, figure 12). The initial sequence of carbon deposit was in a centripetal direction along those channels associated with the bronchi and pulmonary artery.

Connective tissue deposition associated with the accumulation of carbon particles in these sites apparently result in the partial blockage of the normal lymphatic flow for, in lungs containing large amounts of carbon, it was then found around the lymphatics along branches of the pulmonary veins and in the pleura (Plate III, figures 10, 11, and 13). Since the perivenous lymphatics also drain into the bronchial and hilar nodes which may be partly blocked, collateral lymph channels in the pleura help to convey the lymph (and carbon) around the pulmonary segments and lobes to other sources of entry into the main lymphatic channels.

The propulsion of the lymph by the massaging action of the lungs against adjacent tissue is suggested by the deposition of the carbon in the visceral pleural areas adjacent to the intercostal spaces but not that adjacent to the ribs (Plate III, figure 13). There was also little carbon deposited in the pericardial area, around the acute anterior borders of the lungs, or on the diaphragmatic surfaces, as compared with the carbon deposited in the costal surfaces. Injections of the fetal pleural lymphatics also indicated that the lymphatics were more numerous and had a greater number of valves in those areas which subsequently acquired little carbon.

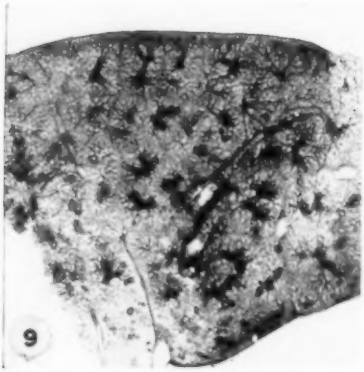
As shown by these studies and reported by Rouviére (5), lymphatics do accompany the smaller branches of the pulmonary artery and pulmonary veins. Normally, with the contraction of the excised lung by its inherent elasticity and the shrinking effect of chemicals used to fix the lung tissue for histologic examination, these smaller lymphatic channels are not seen. However, if serial sections of alveoli or casts of them are studied, it is apparent that an artery and a vein with their accompanying lymphatics make contact with some one part of every alveolus. That lymphatics may drain the alveoli directly was indicated in several instances in which metastatic groups of cancer cells were observed in lymphatics accompanying small branches of the pulmonary artery on an alveolar wall.

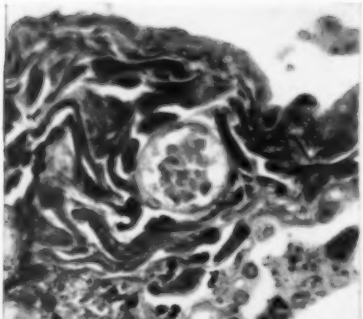
Sections of the pulmonary ligament from cases of pulmonic cancer contained lymphatics in this ligament which established a connection between the mediastinum and the medial surfaces of the lower lobes of the lungs.

The establishment of a definite relationship of the bronchial and tracheal nodes to the lymphatic drainage from particular pulmonary segments is greatly desired, and some information in this field is being accumulated from surgical specimens. However, the experimental animal is better suited to the accumulation of more controlled data and, although the work done on the application of radioactive material into the bronchi of dogs resulted in a variable pattern of bronchial or hilar nodal drainage to the area of instillation, subsequent work, in which india ink was injected into the bronchi of dogs through a bronchoscope, did demonstrate that there is a fairly definite pattern of lymphatic drainage from the various segments of the dog's lung.

In summarizing this part of the presentation (Plate IV) it is concluded that: lymphatics do extend as far as the alveoli; the normal lymph flow (from the carbon and edema studies) seems to be in a centripetal direction along the bronchi and pulmonary artery; the lymphatic drainage from the periphery of the lobules and the pleura is along the pulmonary veins to the hilar nodes; in the event that the nodes or channels are occluded, then the lymphatics within the pleura convey the lymph around the segments to the mediastinal channels; and it has been pointed out that lymphatics do exist in the pulmonary ligament.

How does all of this fit in with pulmonary emphysema? In emphysema, as the air spaces become enlarged, pressure may be applied to certain lymphatic channels and peripheral nodes. Lymph from such diseased areas of tissue would be conveyed mainly by collateral channels in the pleura or along the proximal part of the bronchi and pulmonary artery toward the hilar region. Just as the bronchopulmonary veins are known to become dilated and act as collateral venous





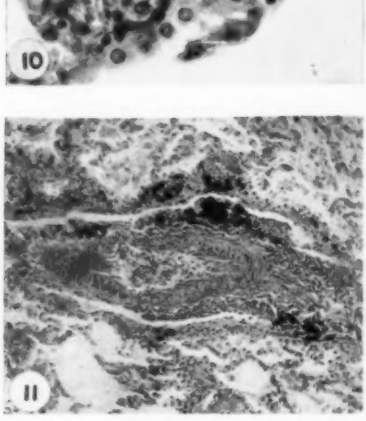


PLATE III

FIG. 9. Cleared section, one-sixteenth of an inch thick, from an air-dried lung of a 59-year-old female who died as a result of a cerebrovascular accident. Note the distribution of the carbon, mainly around the branches of the respiratory bronchioles. (× 1)

FIG. 10. Section through the pleura of a 25-year-old female, whose death was due to uremia. Note the carbon "granules" in macrophages within an alveolus and the large clumps of carbon between strands of connective tissue in the pleura. (× 430)

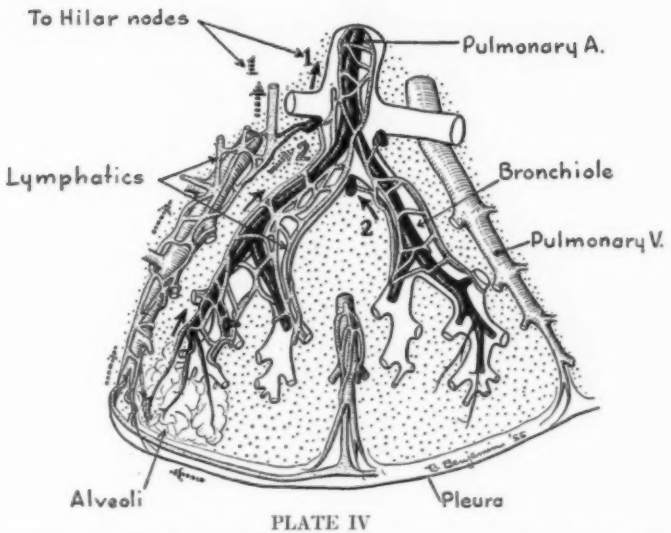


PLATE IV

FIG. 14. Diagram of the lymphatic drainage from two lobules in a segment of the lung. The course of flow in the lymphatics around the pulmonary artery and airways (indicated by solid arrows) is in a centripetal direction toward the hilar nodes (*1*) and bronchial nodes (*2*). The flow in the lymphatics around the pulmonary vein is from the pleura, peripheral part of the lobules and the septa (indicated by cross-stripped arrows). The perivenous lymphatics course along the pulmonary vein to the hilar nodes (indicated by cross stripped 1) or toward the apex of a lobule or segment, where branches of the perivenous lymphatics go to lymphoid tissue at the bifurcation of the bronchi (indicated by cross-stripped 2).

For simplicity of presentation, the structures shown are not of correct proportions. No lymphatics are shown around the branch of the pulmonary vein in the septum at the right side of this figure, and only part of the course of the pulmonary vein and its accompanying lymphatics are shown in the septum between the two lobules.

channels in cases of emphysema, the lymphatics also establish comparable collateral channels to convey lymph.

Consideration should be given to the fact that the lymphatics have the thinnest walls of the vascular channels. If they should become occluded, could this occlusion not lead to edema of the pulmonary tissue, followed by venous congestion, and then partial arterial occlusion? Could the lymphatics be one of the primary structures involved in the initiation of the processes resulting in emphysema?

This afternoon, as I understand it, Dr. Oderr is going to point out to you that he has found a relationship between the formation of emphysematous areas and the position of the lymphatics

PLATE III

FIG. 11. Section from the lung shown in figure 10. Note carbon in the connective tissue along the walls of the lymphatics surrounding a branch of the pulmonary vein. (× 100)

FIG. 12. Section from the lung of a 41-year-old female, who died of cerebral hemorrhage. The carbon particles are deposited mainly along the lymphatics, accompanying branches of the bronchi and pulmonary artery. There are a few scattered carbon deposits in the pleura. Note the carbon in a lymph node, just below the center of this section. The dark color in the lower lobe (right side of figure) is due to post-mortem-dependent congestion of this area. (Section, approximately 500μ thick, furnished through the kindness of Drs. Gough and Wentworth, Welsh National School of Medicine, Cardiff, Wales). (× ½)

FIG. 13. Costal view of an air-dried, left lung of a 71-year-old male, whose death resulted from a cerebrovascular accident. The carbon deposits in the pleura are mainly in the upper part of the lung and their distribution corresponds to the intercostal spaces. Sections from this lung, such as that shown in figure 9, contained large deposits of carbon around the lymphatics and in the nodes. (× ¼)

within the lung. I would like to call your attention to the work of Heppleston (6) who has also shown that emphysema may form around that part of a respiratory bronchiole where we do know that the first lymphoid tissue is found. Just in the way of comparison, Liebow (7) has shown that in emphysema the bronchopulmonary veins are instrumental in bringing blood back into the heart. Here again we have a similar situation. Here we have collateral lymphatic channels which you see in the pleura becoming enlarged to bring lymph back into the general circulation.

I trust that the methods of study proposed here and some of the deductions made from them, will help in the understanding of the lymphatics in pulmonary emphysema and in the future stimulate thinking and investigation concerning them.

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General Discussion

Dr. Gardner Middlebrook (Denver, Colorado): I happen to be interested in air-borne infection at the moment and, in particular, in the transport of mycobacteria in a still viable but not multiplying form through the lymphatics to the regional nodes. In relation to the problems of emphysema, it would seem that, if your observations are integrated, Dr. Tobin, with the suggestions of Reid and May of London (Brit. M. J., 1956, *2*, 1539) and their emphasis upon infection of the terminal bronchioles and, if there is any doubt whether or not an infection occurs there with a distal enlargement of the lymphatics, the whole process of emphysema insofar as it is related to infection could be explained. It seems to me that there would be very little evidence of mediastinal node involvement in persons who die of emphysema in spite of focal infection in the terminal bronchioles. I would like to know whether or not this has been observed by pathologists.

Dr. Tobin: I am not a pathologist and can't answer that; but, to answer your other question about infection at the level of the bronchiole, you must remember one finds lymphoid tissue, not lymph nodes, at the level of the respiratory bronchiole.

Dr. Morgan Berthrong (Colorado Springs, Colorado): I don't think that the lymphatics in chronic emphysema of whatever variety are in any way different or are particularly involved. They are certainly not large, as in lobar pneumonia and in lobular pneumonia, in which there is obviously an infection drainage.

Dr. Otto Brantigan (Baltimore, Maryland): One can read in most anatomy books a description of the bronchial veins. I bring up the question whether or not they are actually present. If we do not have them, where is the run-off of the bronchial arteries and, if the run-off has to be through the pulmonary system, might it not be important to take into consideration in pulmonary function?

I would like to quote to you what meager studies I have made on bronchial veins. First of all, macroscopically, our professor of anatomy tells me that he has never seen one. Dr. Krahl has told me that he has not seen one either. Prominent surgeons, Overholt for example, also tell me that they have never seen a bronchial vein. Students to whom we have given the problem in dissection for the last five or six years have not come up with a description of a microscopic dissection of a bronchial vein. At the last meeting of the American Society for Thoracic Surgery, Dr. Littlefield showed in dogs that, when they tied off the pulmonary artery and the vena cava and kept up the extrapleural circulation, they developed such a high pressure within the pulmonary system that they actually had rupture of the vessels of the capillaries within the lung. Other workers have pointed out this year that, if you are operating upon a heart without a septal defect and do not decompress the left side of the heart, then there is damage from overpressure within the pulmonary capillaries. It seems to me that this is a pretty good physiologic experiment proving that there are not any bronchial veins as they are described in the anatomy books and that we ought to change our thinking in this respect.

Dr. Pratt: With respect to the obstruction of lymphatics by pigment, you may obstruct one but I'm sure that the lung will then rebuild lymphatics

which will drain around this obstruction. Some evidence for this is the fact that in silicosis, with densely fibrous nodes, carcinoma of the lung will metastasize to these silicotic nodes probably by collateral circulation. In addition, we frequently see lungs with very heavy pigmentation without emphysema.

DR. LOOSLI: I would like to ask Dr. Liebow about drainage beyond the hilar nodes in the lung. Does the thoracic duct take part in the drainage? During a study of the pathogenesis of bacteremia in pneumonic dogs, I repeatedly obtained negative cultures from the thoracic duct even though the left lobe was highly consolidated and there was bacteremia. On cannulating the right lymphatic duct I recovered hundreds of colonies in a very small amount of fluid; this led me to consider that essentially all of the drainage from both sides of the chest was either through the thoracic duct or through aberrant vessels which went into little veins which we could not detect. Does the lymphatic duct take a major part of the lymph flow?

DR. M. HENRY WILLIAMS (Valhalla, New York): In respect to the bronchial veins, Alley and Shedd some time ago did an experiment which I have repeated. If one cannulates a lobar pulmonary artery in a dog and then occludes the pulmonary vein draining that lobe, the pressure within the pulmonary artery rises but it does not rise to the level of the systemic pressure. I assume that this confirms what you suggested—that the run-off is small but present.

DR. EISEMAN: Have you seen them?

DR. WILLIAMS: No.

DR. BERTHRONG: I really shouldn't be discussing bronchial veins with Dr. Liebow in the audience, and I'm sure he will mention it at great length this afternoon. In 1944, Ferguson and associates, in a paper on mitral stenosis (Am. Heart J., 1944, *28*, 445), said that they were able to see bronchial veins and to put injection material into them. He also showed them coursing their way along the major bronchi and on to the azygos vein. Microscopic sections of major bronchi in cases of mitral stenosis occasionally show enormous, dilated, thin-walled, veinlike structures in the submucosa. These actually are in a sense bronchial veins, varices along bronchi, and may explain the massive hemoptyses which may occur in mitral stenosis. Dr. Liebow shows these markedly enlarged veins in emphysema, but in emphysema the veins are nowhere near as prominent histologically in the walls of the bronchi as they are in some cases of mitral stenosis.

DR. EISEMAN: I wish to thank you all for getting into the spirit of things. The meeting will resume this afternoon.

PATHOLOGY

DR. JOHN R. DURRANCE, *Moderator*

THE PATHOLOGY OF EMPHYSEMA[1]

KENNETH H. McLEAN

An important aim of this conference is to initiate new lines of thought on the problem of emphysema. In order to emphasize this aim, this presentation is divided into two parts: the first is concerned with observations that any hypothesis of pathogenesis must explain; the second presents the hypothesis that emphysema is a sequel of bronchiolitis.

Requirements of an Hypothesis of Pathogenesis

Study of the macroscopic anatomy of emphysema led to a classification of the morphologic varieties of emphysema (1). The main division was into generalized and localized forms, but this was arbitrary. Some examples of generalized disease were due to multiple local lesions, and a few of the remainder did not show gross variation in the severity of the emphysematous change from one lobule or one subsegment to another. Many lungs show affected lobules adjacent to others which are relatively normal (figure 21). It seems inescapable to conclude that the *basic* lesion is localized, whatever secondary factors may be operating.

Simple inspection of a grossly emphysematous lung reveals that much lung tissue has been destroyed. Not only alveoli-bearing passages, but also larger bronchioles (and vessels of corresponding size) have been destroyed without leaving conspicuous remnants (figure 22). Such observations must be explained by an hypothesis of pathogenesis and, also, they emphasize that emphysema is a more complex problem than simple disruption of alveolar walls.

Histologic study of the lungs of patients with clinical emphysema was not fruitful; structure was found to be so greatly altered that few clues could be obtained to the puzzle of how these changes occurred, and in what sequence (2). An alternative was the study of minimal emphysema with the aim of detecting associated lesions.

Centrilobular emphysema is a common minimal lesion and its anatomy is well known (1, 3, 4). The periphery of the lobule is normal; centrally, there is considerable destruction of air passages involving both the musculo-elastic mesh forming their true walls and the walls of associated alveoli (figure 23). When emphysema is very slight the air passages involved can be recognized as respiratory bronchioles which have lost many of their alveoli, leaving only irregular remnants of the musculo-elastic mesh (3, 5).

In more advanced lesions, such as can be recognized macroscopically, respiratory bronchioles, and even terminal bronchioles, could not be identified positively. For this reason Leopold and Gough (3) refer to the most distal bronchiole with intact walls as the "supplying" bronchiole, from which numerous intercommunicating pathways arise, forming what has been termed a "common pool." From the "common pool," relatively normal air passages continue to the periphery of the lobule.

Of particular interest is the observation that evidence of inflammatory damage could be found regularly in the tissues in the emphysematous region and in bronchioles immediately proximal. Readily demonstrable changes include regions of increased collagen and reticulin, patchy destruction of special tissues, and also partial obliteration of the lumen of an occasional bronchiole.

This evidence of past bronchiolar inflammation, even in minimal lesions of emphysema, made it necessary to know more of the natural history of bronchiolitis (6, 7). This study began with a consideration of homeostasis in the bronchial tree, since the establishment of bronchiolitis largely depends on defective homeostasis.

Homeostasis in the bronchial tree depends on ciliary action, cough, and collateral ventilation, all of which are primarily concerned with the maintenance of patent airways. Mucus (or any other fluid) in the bronchial tree is ordinarily swept as a continuous sheet up to the larynx and pharynx. The overloading of this mechanism re-

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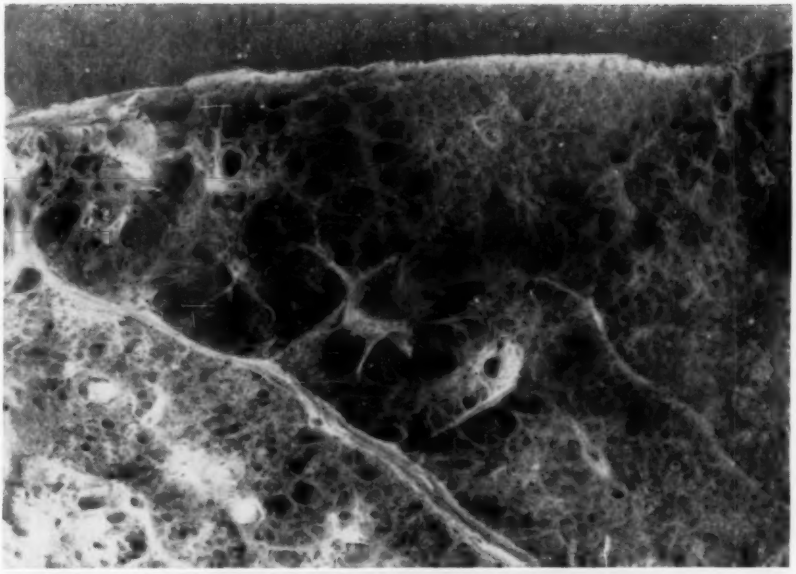

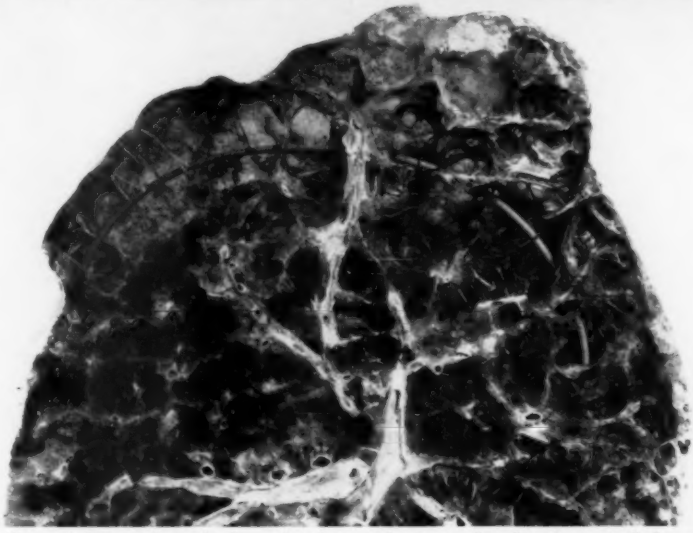

FIG. 21 (Upper). Cut surface of a lung showing emphysema related to two ectatic bronchioles. Elsewhere the lung is relatively normal. (× 3)

FIG. 22 (Lower). The upper half of a sagittally sectioned lung showing gross destruction of lung tissue, involving all structures, including bronchioles, vessels, and intersegmental septa. (× 0.6)

sults in the formation of masses of mucus which may be expelled by coughing but, equally well, may be aspirated deep into the bronchial tree, producing complete occlusion of bronchioles (8). This probably occurs frequently in healthy persons, but ordinarily has no ill effects since the lung distal to the occluded bronchioles is collaterally ventilated from adjacent lung through

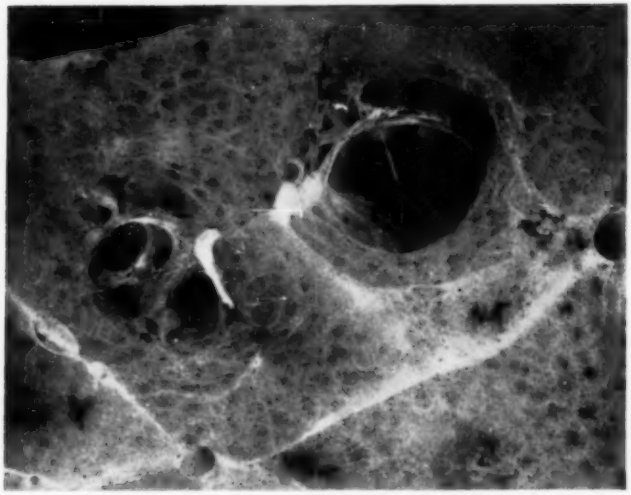

FIG. 23. Cut surface of a lung showing centrilobular emphysema. In each lobule the periphery is unaffected and the emphysema can be seen to be related to the bronchiolar arborizations.

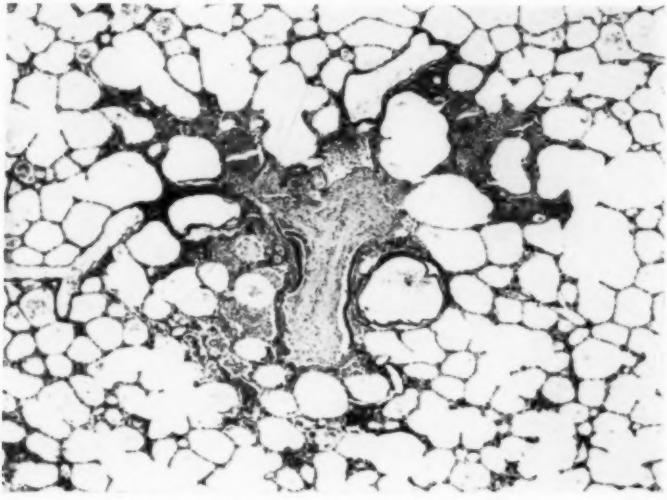

FIG. 24. Section just distal to a terminal bronchiole showing two first order respiratory bronchioles and their immediate branches occluded by mucus; terminal respiratory infection. (Hematoxylin and eosin stain, × 24)

the alveolar pores, and subsequent coughing soon expels these plugs.

Bronchiolar plugs may be of variable length, but regularly extend to the level of the respiratory bronchioles (figure 24). A simple study of normal bronchograms confirms this point, so-called "alveolar filling" being, in fact, bronchiolar obstruction to the level of the respiratory bronchioles (9).

Homeostasis may be defective because of overloading of the mechanisms or because the mechanisms themselves are deficient. For instance, the overload may be due to excessive mucus or ex-

udate in the respiratory tract, and the mechanisms may be directly affected by destruction of cilia, weak coughing, or reduction in collateral ventilation due to shallow respiration or to occlusion of alveolar pores by exudate. In such circumstances bronchiolar occlusion occurs more often and plugs tend to remain *in situ* for relatively long periods.

Considering the situation in a healthy adult (in whom occasional transient bronchiolar plugging can occur), by far the most frequent cause of significant breakdown of homeostasis is infection by the common respiratory viruses. In such episodes bronchiolar plugging occurs freely, particularly overnight when breathing is quiet and cough is suppressed.

These plugs frequently contain nasopharyngeal bacteria and, if expulsion of the plug does not occur rapidly, these bacteria will proliferate and reach a concentration within the plug sufficient to produce an inflammatory reaction in the adjacent bronchiolar wall. In terminal infections there are innumerable plugs of this type, showing leukocytes traversing the mucosa and accumulating, at first, on the periphery of the plugs (figure 25).

It is important to emphasize that bacteria must remain static in the respiratory tract to attain high concentrations and that, ordinarily, only bronchiolar plugs supply this condition. For this reason bacterial inflammation in the respiratory tract occurs maximally at the site of maximal bronchiolar plugging—in the small bronchioles and respiratory bronchioles.

Inflammation of this type tends to persist as long as homeostasis remains defective. Thus, although viral infections are of great importance both as a cause of bronchiolar damage and in predisposing to bacterial bronchiolitis, bacteria of low pathogenicity are an important cause of bronchiolar inflammation and damage because of their potentially long duration of action.

Once bronchiolar inflammation is established, two courses may be followed. First, the plug may be expelled; damage to wall structures may occur but, because of new formation of epithelium, elastic tissue, and perhaps also some muscle tissue, such bronchioles often appear superficially normal. Second, the plug may not be expelled and the lumen may become partly or completely occluded. Significant partial occlusion is less common than complete occlusion, probably because much-narrowed airways are likely to become obliterated in subsequent inflammatory episodes.

If these occlusive lesions are to be studied at an early stage in their evolution, it would be well to examine the lungs of a patient who died following severe bronchiolitis of one or two months' duration; the lungs of children with fibrocystic disease of the pancreas who died after a prolonged respiratory illness provided excellent material of this kind (7). Bronchioles completely occluded by young granulation tissue were readily demonstrable, the smallest bronchioles (particularly the

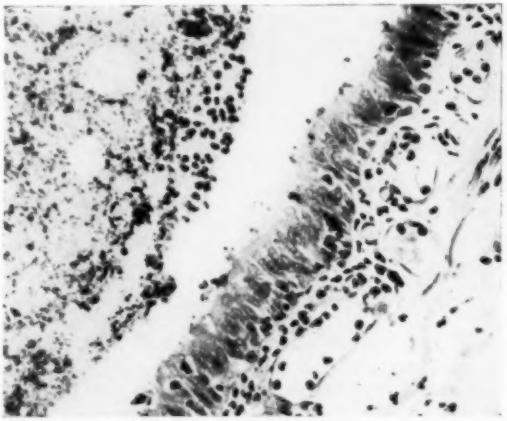

FIG. 25. Section of a large bronchiole which was completely occluded by a plug. This plug (which has shrunk in processing) contains huge numbers of bacteria, and leukocytes can be seen in the submucosa, in the mucosa, and on the periphery of the plug. (Hematoxylin and eosin stain, × 180)

respiratory bronchioles) being most often affected. Usually, more distal passages were not affected and remained aerated by collateral ventilation (figure 26).

When lesions of longer duration were sought, even in the same material, however, bronchiolar remnants were inconspicuous. Similarly, in a bronchiectatic lung it was easy to find a bronchiole which ended blindly; all of its original arborization had been obliterated at some time, but detailed study of such lesions rarely led to the positive recognition of the remnants of obliterated bronchiole. In general, sufficient evidence remained to recognize the remnants of large bronchioles; but alterations in architecture and tissues were such that passages of the size of respiratory bronchioles left no discernible traces of their original structure.

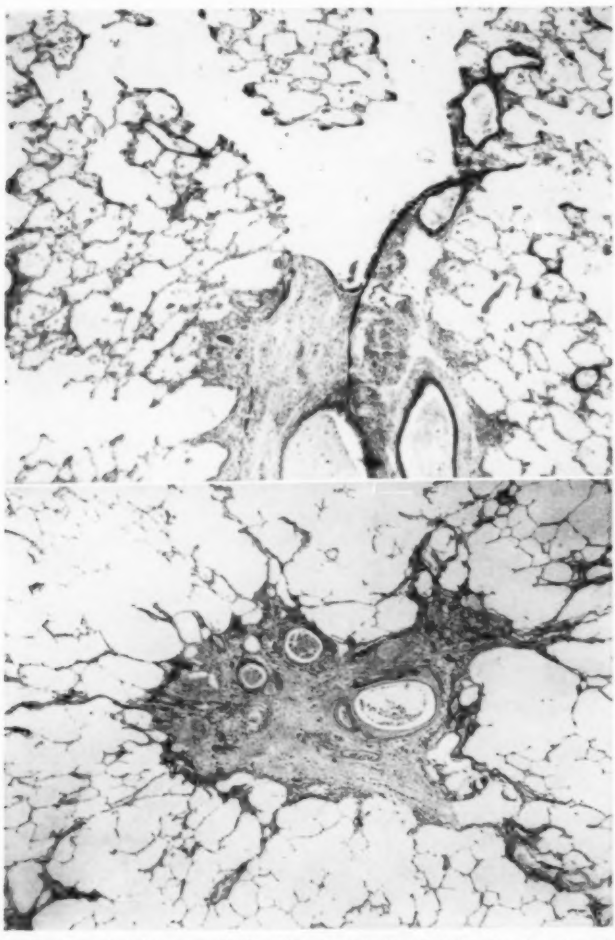

FIG. 26 (Upper). Section showing granulation tissue occluding the lumen of a second order respiratory bronchiole with aeration of more distal passages. The original lumen is outlined by surviving *elastica*; fibrocystic disease of the pancreas. (Elastin stain, × 25)

FIG. 27 (Lower). Section showing a mass of scar tissue which arose in the wall damaging a large bronchiole, branches of which accompanied the small pulmonary artery within the scar (larger vessel at right), following the vascular branches distally; asthma. (Elastin stain, × 14)

Study of emphysematous lungs yielded similar results. Although bronchioles must have been obliterated, search for their remnants was frustrating, and only the remnants of large bronchioles were identified with certainty. Often this was only possible because a fibrous strand arising from the wall of a damaged bronchiole continued peripherally alongside the arborizations of a pulmonary arterial branch (figure 27).

Observations of this type made it difficult to avoid the conclusion that extensive and inconspicuous obliteration of bronchioles occurs in any lung which is damaged by inflammatory processes; this includes emphysematous lungs.

Any hypothesis of pathogenesis must therefore fulfill certain requirements. In summary these are: (*1*) It must explain the nature of the basic localized lesion, the disappearance of bronchioles and vessels as the disease progresses, and the regular association of evidence of inflammatory damage in the small bronchioles and respiratory bronchioles, even in the earliest recognizable lesions of emphysema; (*2*) since respiratory tract inflammation is generally considered to be associated with the disease, the hypothesis must be consistent with the natural history of bronchiolitis; (*3*) the hypothesis must account for the initial lesion. There are many secondary factors which may accelerate the evolution of the disease once it is established. These must not be mistaken for the basic lesion.

The Hypothesis That Emphysema Is a Sequel of Bronchiolitis

In order to avoid confusion due to the operation of secondary factors late in the disease, it is essential to consider first the pathogenesis of minimal lesions, such as the "early" forms of centrilobular emphysema. There are two factors operating in the course of bronchiolitis which may be related to the genesis of these lesions: reduced elasticity of centrilobular tissues, and "air-trapping" beyond occluded bronchioles (2, 5, 10).

Reduced elasticity: Reduced elasticity is a simple concept. Inflammation reduces the elasticity of all body tissues. The respiratory bronchiolar tissues involved in acute bronchiolitis do not present an exception and, when subject to stress, deformation and disruption could result. That this may be a factor is supported by the observation that the more advanced the centrilobular change, the more evident are lesions due to past inflammatory damage.

Yet, this factor alone is inadequate since it cannot explain how emphysema eventually involves the whole lobule. When simple bronchiolitis complicates centrilobular emphysema, the air passages beyond the "common pool" are not involved. Also, it does not take into account the pressure gradients created by "air-trapping" beyond obstructed bronchioles.

"Air-trapping": The significance of "air-trapping" has rarely been considered, and little is known of the nature of the local stresses that are created in the lung as a result of bronchiolar obstruction. Collateral ventilation can be relatively efficient in that a high proportion of bronchioles must be occluded before hypoxemia results, as was shown by Van Allen, Lindskog, and Richter (11). Yet, these same workers demonstrated pressure gradients on expiration between collaterally ventilated and normally ventilated parts of a lung, and that these gradients increased greatly in the release phase of coughing. (In the absence of bronchiolar obstruction, intrapulmonary pressure gradients are small, and coughing puts little stress on lung tissue.) Presumably, this "air-trapping" on expiration is due to narrowing of the tortuous passages and of the alveolar pores through which air reaches collaterally ventilated areas.

Thus, after a cough, a sizeable pressure gradient develops between passages beyond obstructed bronchioles and neighboring normally ventilated lung. This stress will recur until the bronchiolar plug is expelled or until the pathway of collateral ventilation is rendered freer by breakdown of tissue.

How this breakdown might occur is conjectural. It may be an acute process operating during inflammatory episodes; the occurrence of interstitial emphysema in infants with severe bronchiolitis implies that the forces involved are sufficient to disrupt tissues. On the other hand, it is possible that the elasticity of the tissues may be affected by ischemia due to capillary compression.

The hypotheses include the assumption that reduced elasticity due to inflammation and the effect of "air-trapping" both operate during the exudative phase of acute bronchiolitis and that much of the change that is recognized subsequently as emphysema occurs during this phase.

However, in such episodes a number of bronchioles are obliterated and, if the air passages beyond such bronchioles are aerated, their aeration depends on collateral ventilation. It would be expected that emphysematous change would follow in these air passages and that abnormal air pathways to the area would be established.

With repeated inflammatory episodes, each resulting in more obliterated bronchioles, the pattern of "air-trapping" would change repeatedly, and more and more lung tissue would be disrupted. The end result is the formation of a new organ which structurally (and functionally) bears only a superficial resemblance to normal lung.

Comment

There are several aspects of emphysema upon which this hypothesis does not touch, such as the sex difference and the observation that emphysema often affects the upper parts of the lung predominantly. Furthermore, the patient with emphysema who has never had a memorable chest infection and who has no cough apparently denies this hypothesis. Yet, whenever the lungs of such patients were examined abundant evidence of past bronchiolar inflammation was found. Indeed, examination of macroscopically normal lungs of adults regularly showed a mild degree of diffuse bronchiolar damage. Therefore, it was concluded that some bronchiolar damage occurs in the course of the common respiratory infections and that in some persons repeated minor infections can produce enough damage to cause clinical emphysema.

The principal reason for the hypothesis is to stimulate thought. This particular hypothesis may be shown to be partly or wholly wrong, but from it derive three definite and valuable conclusions: First, further study is needed of the natural history of acute bronchiolitis; second, there are only a few observations on the mechanics of collateral ventilation and on the genesis of local pressure gradients within the lung; finally, study of this set of problems will provide important information about the enigma, emphysema.

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General Discussion

Dr. Berthrong: I might say that I have not made 20,000 sections of emphysematous lungs. Dr. McLean's thesis that the respiratory bronchioles and the terminal bronchioles are the primary site of pulmonary infection and, therefore, are most apt to show the changes leading to their obliteration is one important concept that he has brought before us today. We have looked over all of the specimens of lungs which were the site of pulmonary infections which we have examined at autopsy in Colorado Springs. In lobar pneumonia we find absolutely no difference in the involvement of the respiratory bronchioles as compared to the immediately adjacent air spaces. The terminal bronchioles in lobular pneumonia, which were found in about 25 to 35 per cent of all autopsies, were in no way more involved than were the smaller bronchi or even the larger bronchi. Viral infections, which are undoubtedly exceedingly important in predisposing to pulmonary bacterial infections, involve the upper air passages at least as severely as the lower. Ulcerative lesions of the larynx, trachea, major bronchi and occasionally of the bronchioles are seen in influenza and other viral infections. In asthma the small bronchi are just as much involved as the terminal bronchioles, probably more so. Mucous

plugs are present throughout the bronchial tree in typical cases of asthma. There is no specific localization. When these are infected, the smaller bronchi are involved as well as the bronchioles. In reviewing the relatively normal lung, which is an important thing to do (as Dr. McLean has emphasized), we have been unable to see any greater degree of bronchiolar infection or inflammation or scarring than could be found in the smaller bronchi. I would also point out that in all cases in which accumulation of mucus or drainage occurs, the lower posterior segments are those most involved. This is seen constantly in the elderly patient or in the postoperative patient. These are the areas perhaps least involved by emphysema. So in one respect I have to disagree with Dr. McLean that the bronchioles of the lung are selectively involved by infections to a greater degree than the bronchi.

As far as obliteration of the bronchioles is concerned, there is no question that there are conditions of obliterative bronchiolitis, an entity which has been known in children and was called "capillary bronchitis or bronchiolitis." The lesions which Dr. McLean pictured in his articles as unequivocal bronchiolar obliteration were found in those patients as well as in patients with asthma. The pictures were not from emphysema patients! Whether they are really present in sufficient numbers to account for emphysema—lobular or otherwise—remains to be proved. I think Dr. McLean will agree with this because he has written that he has *never seen* obliterative bronchiolar lesions in emphysema. Dr. McLean has stated that he believes that the bronchioles have disappeared. Whether this means that they have been obliterated or whether this means that they have been taken into a dilated air pool is a point which also remains to be proved. I wonder whether we could imagine enough bronchiolar obliteration to have even the focal, not to mention the diffuse, emphysema without *ever seeing* these lesions. I personally want to see the actual occlusion before I formulate a theory. Until I *see* it, I can't accept its presence. I would accept the hypothesis that in an area of scarring in the lung, which might have been organized pneumonia, tuberculosis, et cetera, occluded bronchioles may be seen. I take exception with Dr. McLean only because I believe that this is not the time to assume that the lesion causing emphysema of a diffuse or focal type is indeed an obliterative bronchiolitis because I have not seen it and because I do not believe that Dr. McLean has actually seen it.

From a general pathologist's approach to emphysema, I would like to make two more comments. It seemed to me, as I listened this morning, that, despite all warnings which have been given here today, we are still discussing a *group* of diseases, which may result in an irreversible distention of air spaces, as a *single* disease. If we are going to talk about the physiology of air movement or surface tension factors or blood chemistry or ventilation, this is all right. In these circumstances we may discuss irreversibly overdistended air spaces and make good sense. But if we are talking about etiology and pathogenesis, then this is utterly wrong because it may well be that a dozen or more different explanations are possible for these irreversibly overdistended air spaces. It seems very reasonable to consider that the overdistended lung of an old thoracoplasty and inactive chronic tuberculosis without any residual tuberculosis in the remaining lung at the end of twenty years has led to the clinical picture of emphysema. Dr. Ryder recently had a patient who, because of dyspnea, could not walk from his bed to his bathroom. I found no tuberculosis in the remaining lung; the other lung was totally destroyed. The patient had classic emphysema in his remaining lung, but I cannot help but believe that this was of entirely different etiologic pathogenesis than most bilateral emphysema. The focal emphysema around focal scars in the lungs, which is seen so beautifully in healed apical tuberculosis, does not need to be the same emphysema which is seen in patients with bronchial asthma or in patients with kyphotic chests, et cetera. To assume at this point that we have pinpointed the lesion may be utterly wrong. We must for the moment remember that emphysema may be an end point of many different pathogenetic mechanisms.

DR. BRISCOE: Dr. McLean has described the lesion that Laennec referred to as "dry catarrh" in the etiology of emphysema. The lesions in the alveolar walls have always been more obvious than those in the smaller bronchioles, but the latter may be of more importance in causing the obstruction that is characteristic of the disease. This chronic diffuse bronchial obstruction is what is measured physiologically, and what is treated clinically with antimicrobials, dilators, steam inhalations, et cetera. The alveolar wall is not treated. In short, I agree with Dr. McLean and congratulate him on being a physiologist's pathologist.

DR. DAYMAN: At this point in the discussion we can profitably recall that Laennec, whom you cited, reflected carefully and at length on airway obstruction as a basis for pathogenesis and for deranged function. He likened the airway to the "valve of an air gun." But this posed a problem—the same problem which faces us today. Just why was the airway a one-way valve? Why did mucus, the poppet of the valve, seat only on expiration? There was no valve seat as Dr. Laennec saw it. After considering the possibilities, he came to the

conclusion which is expressed in standard references to this day. I shall not complete the sentence, which must be familiar to you, but it contains the phrase: "since the muscles of inspiration are more powerful than those of expiration. . . ." This erroneous notion at times is expressed within a few pages of the place where Valsalva and Mueller pressures are cited to refute the previous statement. Equally erroneous is the notion that expiratory pressure applied to a system of chambers within the same enclosure can cause distention of one chamber while the others are deflated. This is an elementary application of Pascal's law. The mechanical basis for the dehiscence of walls interposed between air spaces in the lung, the essential lesion of anatomic emphysema, must be discovered in the physical conditions accompanying inspiration. Such conditions have been shown to exist when numerous focal areas have been excluded from participation in the process of distention, and thus the adjacent tissue not only must bear the whole burden of stretch but must do so with a disordered elastic network. The same thing happens when a piece of strong cloth is employed to cover the hole in a piece of well worn linen. When stressed, the fabric tears around the patch. In fact, it is difficult to produce recognizable tears in the lungs of experimental animals unless such focal areas are present in abundance.

Dr. Joseph Gordon (Albuquerque, New Mexico): My remarks refer to the relationship of infection to the problem of the development of emphysema. Over a number of years of doing bronchoscopies on patients with bronchitis (and some, of course, who had emphysema), it is most uncommon to have cultures of bronchial secretions show organisms from the lower bronchial tree. In the upper portion of the bronchial tree above the tracheal carina, evidence of infection can be found, but below that level it is most uncommon to find bacteria. This was pointed out many years ago by Chevalier Jackson and has been verified. It is also true in a tuberculous cavity. Over the years when it was popular to do cavity drainage, secretions were collected from the tuberculous cavity and they rarely, if ever, showed organisms other than *M. tuberculosis*.

With regard to the demonstration of occlusion, rarely is any obstruction shown in bronchiectasis which may also be associated with emphysema. Evidence of obstruction is almost never found, though we do have evidence of change in the bronchial tree because of a number of associated factors. I should like to suggest that we consider developmental defects which must play a role in this organ. There is so much time for the completion of the development, even extending to a postnatal period of seven to twelve years of age. We see developmental defects in many other organs which are not so complex as the lung. We do not yet know the normal.

Dr. Fishman: I should like to underline Dr. Berthrong's remarks. We need a clear definition of the term "emphysema." Until this is accomplished, we shall continue to conceal a variety of diseases by one name and to obscure diverse etiologies and pathogenetic mechanisms. For example, Dr. McLean may have identified one such mechanism which may apply to one type of "emphysema"; but such a mechanism obviously cannot be applied to other types.

Dr. Edward Gaensler (Boston, Massachusetts): I come from a city where pathologists now show relatively little interest in the lungs. One of several reasons is their feeling that microscopic observations, particularly in asthma and emphysema, often do not reflect the patient's difficulties or the cause of eventual demise. Perhaps the type of study which we have just heard eventually may give us a clue concerning pathogenesis. It cannot give us an answer to the physiopathologic difficulties.

The lung, unlike the liver or kidney, is an organ of motion. In the kidney, destruction or alteration of cells or conducting passages may well correlate with the clinical picture and the degree of dysfunction. This is not so with the lung. The obstruction in emphysema, and even more in asthma, is largely functional: it occurs while gas is moving, chiefly, as the result of pressures necessary to make the gas move. Obstruction may be minimal during quiet breathing and almost complete during forced breathing. It may be small with breathing at the top of the lung volume and severe with breathing at functional residual or lesser volumes. No wonder that observation of immobilized, fixed, and rigid lung tissue may lead to argument concerning the presence or absence of obstruction, or the relationship between such minor obstruction as may be seen and the clinical difficulties. Asthma illustrates this best: a young patient may have died because he no longer could perform the enormous work required for resting ventilation; yet, after death a practically normal lung may be seen under the microscope.

Dr. McLean has described certain changes in so-called dry emphysema in which he cannot see bronchiolitis or bronchitis. I wonder whether these changes may not be the result of a disease in which maximal effective air flow is reduced to a small fraction of normal, and maximal resistance to breathing may be thirty times greater than normal? May not cough and other mechanisms for establishing homeostasis have become so impaired that these changes terminally may be the result, rather than the cause, of chronic obstructive emphysema?

PULMONARY EMPHYSEMA WITH SPECIAL REFERENCE TO VASCULAR CHANGES[1]

AVERILL A. LIEBOW

Introduction

It is necessary to construct, insofar as possible on the basis of actual observations, a conceptual framework of the pathology and pathogenesis of pulmonary emphysema before considering the vascular changes. This task is made difficult by lack of knowledge of anatomic detail, especially in quantitative terms and as it is in the living; by the reversible nature of certain mechanisms, such as obstruction of bronchioles by mucus; and by the indubitable existence of important functional phenomena such as bronchospasm or vasospasm that may not be reflected anatomically. It is also possible that several mechanisms may be necessary in the evolution of pulmonary emphysema and that these may differ at various stages in the development of the lesions. Consequently, much remains hypothetical, and disagreements in interpretation among different observers have been wide and virulent (1–9).

For present purposes, emphysema will be defined as an overexpansion of distal air spaces, usually accompanied by loss of the septa among them. "Distal air spaces" is used to imply that, not only alveolated substance, but also distal orders of bronchioles, may be involved in any of these processes. In particular, what is referred to as a "bulla" usually represents a much more proximal distribution than that of a single respiratory bronchiole. Transitions exist to "honey-comb lung" brought about, in part, by ingrowth of bronchial epithelium into altered air spaces by way of the canals of Lambert (10). In many instances there are superimposed, to a varying extent, additional lesions such as focal fibrosis and bronchiectasis. These produce deviations from the pathology and pathophysiology characteristic of emphysema as just defined. Insistence that emphysema be defined in other than anatomic terms is as logical as to consider that a myocardial infarct is not an infarct unless it produces the symptoms of substernal pain or the signs of congestive heart failure.

The interpretation of anatomic changes must be tempered by the foreknowledge that many of the functional disturbances in emphysema are reversible and by an appreciation of the very great reserve of the lung. Extensive focal lesions can be tolerated, but a relatively slight diffuse change involving the respiratory surface or vascular bed may have profound functional consequences.

Observations

Aspects of the Mechanics of the Lung in Function

It will facilitate the discussion of some aspects of pulmonary emphysema to conceive of the lung as composed of interlacing sheets of elastic fibers, the walls of the alveoli, which are always on the stretch. It must be acknowledged that "elastic tissue" is not the only material in the lung that exhibits elastic properties, but the basic concept is nevertheless useful. Moreover, important surface tension phenomena are ignored. This stretch results from the fact that the lung is made to fill a space larger than the size it assumes when free; consequently, it is always tending to collapse. The elastic fibers are attached to the visceral pleura and to the interstitial tissue that embeds the vessels and bronchi to which they give a tractional support. This support failing, bronchioles unsupported by cartilage tend to collapse, especially in expiration—an important mechanism in air-trapping. A pull depending upon the degree of stretch is, therefore, constantly exerted on all of these structures. When the thorax is made larger by the forces of inspiration, the pull upon the pleura becomes greater. This pull is a force tending to draw the visceral pleura away from the parietal pleura and produces the "negative intrapleural pressure"; the greater the pull, the more negative the pressure. Thus, the intrapleural pressure is more negative during the inspiratory phase. These statements, paraphrasing as they do concepts clarified by the Macklins (11), may seem unnecessarily elementary. The "negative intrapleural pressure" is, however, widely misunderstood as a mysterious vacuum. Actually, it has no meaning except as a reflection of the retractile force of the tissue which produces it.

The increased pull of the elastic tissue during the inspiratory phase is exerted also upon the

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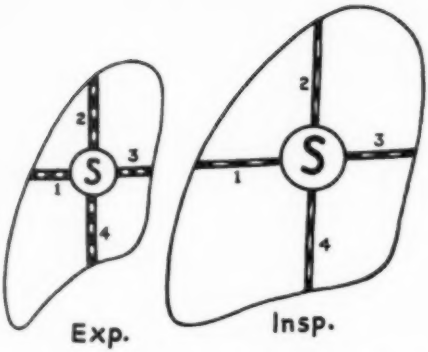


FIG. 28. Elastic fibers (of which four of many millions are shown) that compose the interalveolar septa of the lung are always on a stretch. This increases as the thorax enlarges during inspiration, with a consequently greater pull on the pleura and on any structure, "S," such as a vessel, to which the fibers are attached. "S" can enlarge in this instance only by receiving more blood. "S" could also represent an alveolus or bronchus or a pore of Cohn, any of which also experiences an inspiratory increase in size. The capillaries, however, lie *within* the elastic substance of the interalveolar septa and tend to become flattened with elongation and attendant thinning of the fibers.

bronchi and vessels (figure 28). The inspiratory increase in caliber and length of the former has been demonstrated by bronchography. Since the latter contain an indistensible medium, they can yield only by acquiring a larger content of blood; hence, the blood-pumping action of the respiratory movements. Flow in the appropriate direction is assured by the valves and the action of the heart.

On the contrary, since the capillaries are enclosed *within* the elastic sheets of the alveoli, they become elongated and flattened, as these fibers are subjected to inspiratory stretch—and consequent thinning. Flattening beyond a critical point may be sufficient to result in the squeezing out of blood and in an impediment to inflow.

Classification of Pathogenetic Mechanisms of Pulmonary Emphysema

Even the briefest study will indicate that pulmonary emphysema is not a simple process but, in most instances, the result of a conspiracy of several forces. In general terms, the distal air spaces can be overdistended by a pull from without, by a push from within (air-trapping), by the loss of the septa among them, or possibly by a relaxation of their walls resulting from a change in the quality of the material of which they are composed. These possibilities are listed in table 1 and will be discussed subsequently. Some are illustrated in figure 29.

Traction

If it be assumed that the thorax is a more or less rigid box, then shrinkage or ablation of a part of its contents will produce an increase in the size of other parts that can so accommodate. The tissue most competent to yield is the lung. Such accommodative overexpansion of the lung tissue has been called "compensatory" emphysema. The "compensation" clearly has relevance to space. Compensation is also, in some measure by increased function of the residual parts, a reflection of the fact that only a part of the total capacity of the lung is normally in use. One limit to compensation is possible overexpansion of alveoli with compression of capillaries in the overstretched walls. This is indicated by the fact that, if the total output of the right heart in dogs is restricted to a single lobe, the pulmonary arterial pressure remains lower if overdistention of the lobe is prevented (12). The mechanism is suggested in figure 28. Actually, such extreme overdistention of the lung by traction is very uncommon in man.

TABLE 1
PATHOGENETIC FACTORS IN EMPHYSEMA

I. Traction
  A. "Compensatory"
    1. To atelectasis
    2. To fibrosis
    3. To surgical ablation of lung tissue
  B. To enlargement of the thorax
II. Obstruction of air passages (diffuse or focal)
  A. By mucus
  B. By muscle spasm
  C. By muscle hyperplasia
  D. By fibrosis of bronchioles
    1. Mural
    2. Intraluminal
  E. By stretching and distortion as bullae enlarge
  F. By loss of tractional support of bronchioles with expiratory "valving"
III. Destruction
  A. By necrosis or atrophy
  B. By tension beyond obstruction (?)
IV. "Loss of elasticity" (?)

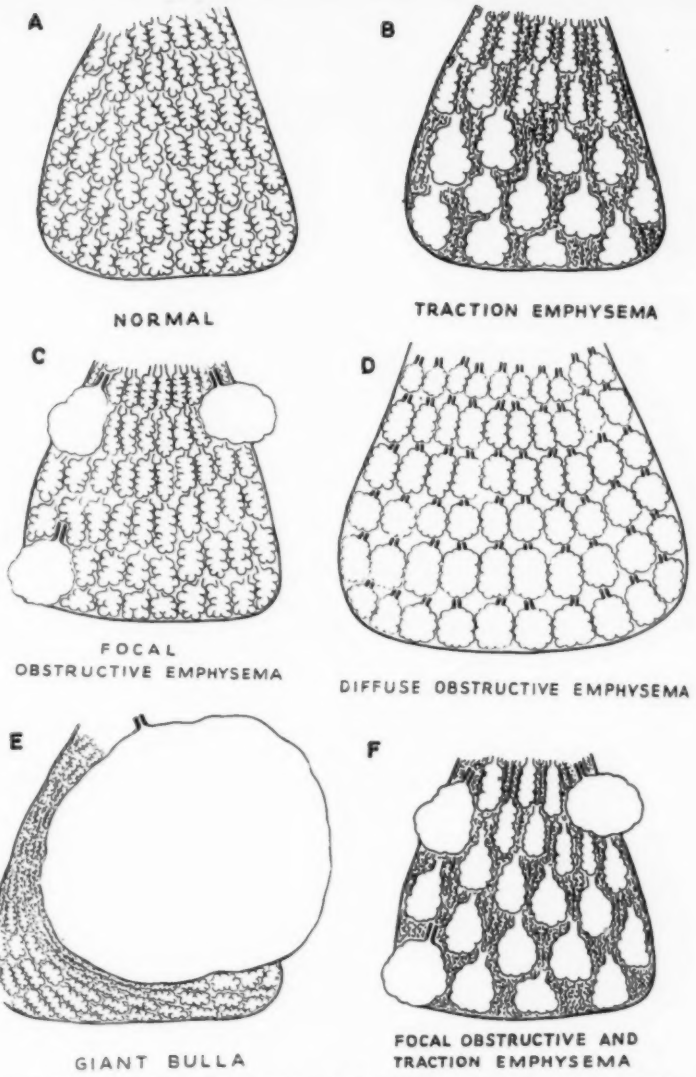


FIG. 29. Schematic representation of various types of pulmonary emphysema in comparison with the "normal": *A*. normal lung: "Distal air spaces" are shown to have thin walls and widely patent lumina. *B*. "focal traction emphysema": There is focal overexpansion of some distal air spaces resulting from compaction of other masses of alveoli focally, either in consequence of atelectasis or fibrosis. The overexpanded alveoli are unobstructed. The lung is shown as if unchanged in size; actually, it tends to shrink and other contents of the thorax are drawn toward the affected side. *C*. "focal obstructive emphysema": In consequence of partial obstruction, either of a valvular or of a rigid type, air-trapping has occurred with massive overexpansion of some distal air spaces. Bullae have formed, several of which are shown bulging above the pleural surfaces as they appear when the lung is removed from the thorax. Obviously, this is not true when the lung is within the intact chest. *D*. "diffuse obstructive emphysema": The process is analogous to that in *C*, but less distention and air-trapping can be tolerated without death if all portions of the lung are involved than when the process is focal. A relatively slight degree of diffuse obstruction can produce much more significant functional difficulty than massive focal obstruction. *E*. "giant bulla": The obstructive, and a concomitant destructive, process is localized, but is so extreme that much otherwise normal pulmonary substance is atelectatic and immobile. This condition can be relieved by extirpation of the bullae, for which reason the condition is sometimes called "surgical emphysema." *F*. "focal obstructive and traction emphysema": A composite of *B* and *C* to indicate that several factors may coexist in the genesis of emphysema. Obstructive emphysema tends to relieve traction phenomena.

The important destructive and, possibly atrophic, lesions are not illustrated in this series.

Compensatory emphysema occurs in atelectasis, whether so massive as to involve one or more lobes, or focal, as in failure of expansion of the lung in the newborn; or in the presence of fibrosis of other parts of the pulmonary substance; or if lung tissue is removed surgically. Under all of these circumstances, the expansile force is traction from without. There is no obstruction of the expanded air passages (figure 30). The total size of the chest tends to be reduced and, if the process is severe, retraction of intercostal spaces may be observed. In the presence of focal contracting lesions, the effect of the traction is greatest on the immediately adjacent air spaces. This is one factor in "perifocal" emphysema, i.e., emphysema in the immediate vicinity of scars. Such a traction mechanism has also been invoked to explain the emphysema associated with the deposits of pigment in "coal-workers' pneumoconiosis," in which there is thickening of respiratory bronchioles but little or no massive fibrosis (13).

Scarring may result not only in traction upon other parts, but also in "retraction." The latter implies simply shrinkage of tissue with enlargement of the air space into which it formerly projected, no pull being exerted on surrounding parts (figures 31 and 32). Such a process can involve progressively more proximal structures should they be rendered discontinuous by atrophy or necrosis (*see* below).

Relation of traction emphysema, bronchiolectasis, and bronchiectasis. Fine interstitial scarring or the organization of minute foci of pneumonia often associated with bronchiolitis may produce pulmonary emphysema of the traction type; contraction of larger masses of granulation tissue distributed about bronchioles in foci of sufficient number and size may exert sufficient force to distend them—bronchiolectasis; ectasia of larger bronchi may result from organization of a necrotizing pneumonitis that produces obliteration of the next distal order of branches and much of the parenchyma beyond, by scarring It may be that impairment of the resilience of such bronchi is also necessary for traction to become effective. Some details of this process have been discussed elsewhere (14, 15). The ultimate result depends upon the size and distribution of the scars.

Under all of these conditions, the initiating lesion is necrosis with an appropriate mass and distribution: minimal when it precedes emphysema, of large extent when it results in bronchiectasis. It must be emphasized that a considerable mass

FIG. 30. Cast in "traction emphysema." Free communication of proximally open, with distorted and enlarged distal air spaces. (× 2)

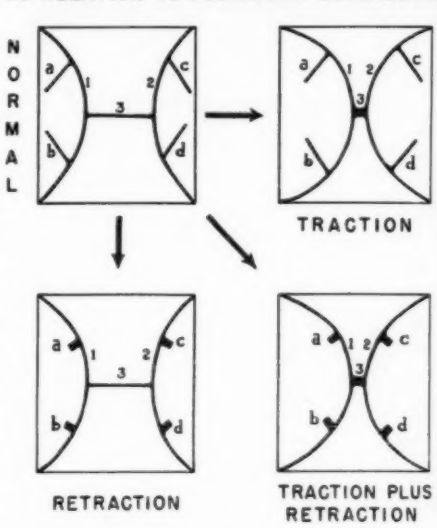


FIG. 31. "Traction" and "retraction" phenomena in the distal air passages. In this diagram, 1, 2, 3, and *a* to *d* are conceived to represent the walls of distal air spaces; 3 is attached to 1 and 2 in such a way that, if it is caused to contract as a result of fibrosis, a pull will be exerted on 1 and 2, whereupon the distal air spaces outlined by 1 and 2 will become overexpanded by *traction*; *a* to *d*, however, project into the lumina of distal air spaces in such a way that, when they are involved in fibrosis, they merely shrink—a process of *retraction*. A combination of these mechanisms is relatively frequent. In the event that walls of distal air spaces are rendered discontinuous, retraction may contribute to their progressive enlargement. *See*, for example, figures 46 and 47.

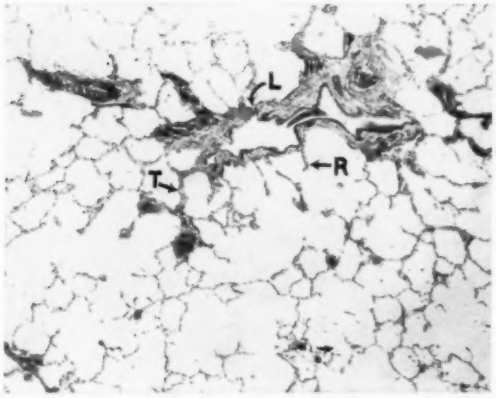


FIG. 32. Traction and retraction phenomena in early stage of emphysema; chronic bronchiolitis with associated changes in the alveoli that attach to the bronchiole. Many of these alveoli have become thickened, presumably from organization of a predominantly interstitial alveolitis in continuity with the bronchiolitis. Certain alveoli (*T*) remain in attachment to others. Contraction of the excessive fibrous connective tissue in *T* would exert a pull on other adjacent alveoli, with "traction emphysema." Some interalveolar septa remain as spurs (*R*) which will suffer "retraction" as the scar tissue shrinks. At *L* is a canal of Lambert through which epithelium is growing in continuity with that of the lumen. (× 30)

of necrotic pulmonary substance may leave only an inconspicuous scar.

Parenthetically, another type of fibrosis should be mentioned which is interstitial (involving septa among the distal air spaces) and which is both so extensive and productive as to persist without marked shrinkage. This reaction can be produced by inhaled metallic agents, such as mercury, cadmium, and (in some instances) by beryllium and by unknown causes ("Hamman-Rich disease").

Enlargement of the thorax as a possible mechanism of traction: There are some who believe that the "barrel" chest often observed in persons with advanced emphysema can result from changes in the vertebral column associated with arthritis of such nature that the thorax is forced into a position of inspiration. This stand has been taken by Loescheke (16, 17), and his reasons have been clearly stated and well illustrated. The emphysema would then be interpreted, at least in part, as the result of a traction mechanism. The question is pertinent, however, whether the barrel chest may not be an effect of enlargement of the lung produced by certain other types of emphysema, such as the obstructive forms.

A traction mechanism is indeed exhibited on a local basis in severe kyphoscoliosis in which there is no doubt that the skeletal changes come first. The deformity can be so severe that the aorta is actually bent upon itself at a right angle (figures 33 and 34). The lower lobes are compressed into the conical apex of the gibbus and are in a state of atelectasis, while the upper lobes are made to conform to the mouth of the greatly overexpanded, more or less cornucopia-shaped chest. The lungs maintain their deformity upon removal from the thorax. Study of casts reveals that the large vessels and bronchi, at least, accommodate by appropriate foreshortening or elongation without obstructive angulation. Superimposed upon the overexpansion of the upper lobes in such persons are the consequences of repeated bronchopulmonary infections, which are probably abetted by the mechanical disadvantage in clearing the respiratory passages by coughing.

Obstruction

Much functional evidence exists of air-trapping in some forms or stages of pulmonary emphysema (18, 19). This is reflected in spirograms of certain patients who, when asked to breathe deeply, will show a displacement of the resting level of the pulmonary gas content increasingly to the position of inspiration. The particular difficulty with the expiratory phase experienced by many

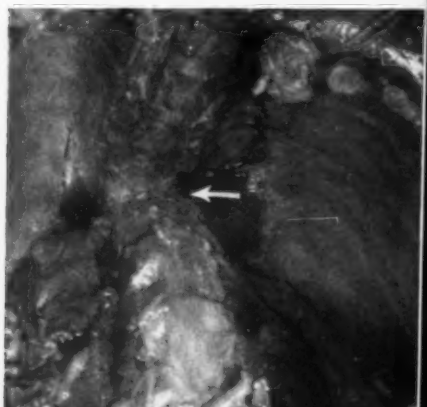


FIG. 33 (Left). Thorax in kyphoscoliosis. The thorax narrows in a conical fashion posteriorly toward the bend in the spine (arrow), but flares remarkably anteriorly.

FIG. 34 (Right). Cast of lung that filled the chest shown in figure 33. The right angle bend of the aorta is marked by an arrow to correspond to the gibbus shown in figure 33. The lower lobes (to the left of the white line) are atelectatic. On the contrary, the upper lobes are markedly overdistended, both in the anteroposterior and vertical axes.

patients is in itself evidence of the tendency to trap air. Anatomically, the outward bulge of bullae, their failure to collapse in many instances when the lungs are removed from the thorax (figure 35), and their actual resistance to deflation are further signs of air-trapping. This can sometimes be demonstrated at the operating table: When positive pressure anesthesia is interrupted, the lungs collapse, except for the bullae (figure 36). Under the microscope, outward displacement and compression of surrounding relatively normal tissue are often evident.

Some large bullae, however, communicate freely with the proximal air passages. This may be either because a former obstruction has been relieved or because the bullae were produced by some other mechanism—for example, destruction.

Air-trapping is sometimes the consequence of anatomically demonstrable bronchostenosis. This may be rigid or valvelike and, specifically, expiratory. Bronchostenosis is sometimes evident in casts (figures 37–39).

Under certain circumstances, rigid stenosis of bronchi or bronchioles can produce trapping of air. When the pressure in the proximal tracheobronchial tree is sufficiently increased, as in the compressive phase before coughing, air is forced momentarily into the air passages distal to the obstruction where, not being freely vented, it will expand during the relatively long nonexpiratory phases.

Among the irreversible changes that favor air-trapping is mural fibrosis of bronchioles sufficient to restrict the lumen (figure 40). This lesion has been emphasized by Amberson and Spain (20) and by Spain and Kaufman (21). The principle here is that the scar tissue is sufficient in mass so that its contractile force succeeds in narrowing the lumen about which it is disposed in the manner of a sleeve. Under these circumstances, the fibrous tissue may also be relatively unyielding to inspiratory traction. Such lesions, however, are not constantly found in pulmonary emphysema.

The effect of bronchostenosis in the trapping

of air under pressure is exemplified in a recent fatality in a submarine-escape training tank.

A young submariner died of air embolism after coming to the surface from a depth of 50 feet. He was found to have a broncholith obstructing a segment of the left lower lobe. When at depth, air had become forced behind the obstruction at a pressure equivalent to that of 50 feet of sea water. As he ascended, the trapped air expanded but could not vent freely and, when a critical point was reached, forced its way into the interstitial tissue of the lung and pulmonary veins. Behind the obstruction were chronic emphysema and evidence of chronic bronchiolitis and pneumonitis.

Interstitial emphysema is a complication of any form of obstructive emphysema in which air becomes trapped under sufficient pressure. Recent experimental studies reveal interstitial emphysema to be a function, not only of the absolute pressure, but also of the degree of distention of the lung (22).

A second and more common mechanism is sufficient restriction of the lumen during the expiratory phase. Poiseuille's law, which states that resistance to flow of fluids in rigid tubes is inversely proportional to the fourth power of the radius, has been invoked to explain the relatively great increase in resistance to air flow with a relatively slight decrease in the lumen (23). It does not apply exactly to compressible fluids (respiratory gases) in variable nonrigid tubes (the bronchi and distal air passages). The lesions in the respiratory tree may sometimes take the form of a flap or ball valve, as in the case of certain tumors, polyps, or masses of exudate. A special form of valving may be consequent to loss of tractional support of bronchioles. It has already been indicated that traction upon the smaller air tubes, if they can yield, is greater upon

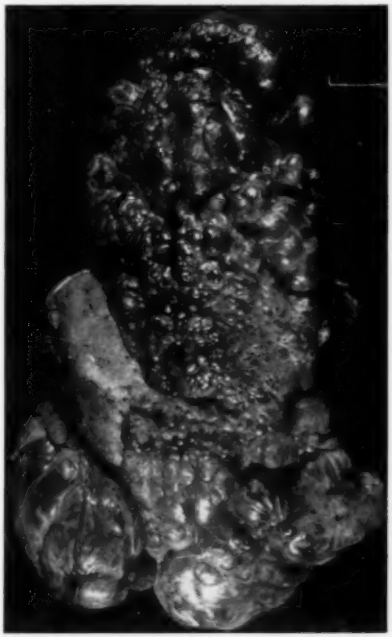


FIG. 35. Lung with bullous emphysema after removal from the chest. The bullae remain distended. Marked loss of pulmonary substance has occurred.

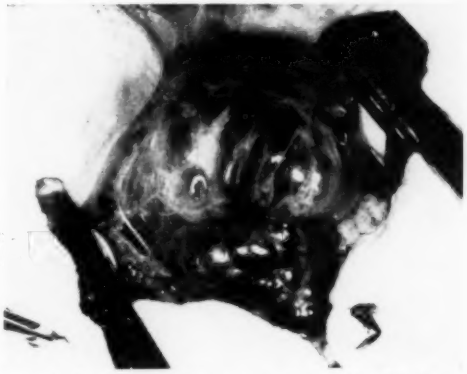


FIG. 36. Bulla replacing most of an upper lobe as seen at operation. It does not deflate when the positive pressure in the anesthesia apparatus is reduced (*compare* with figure 48).

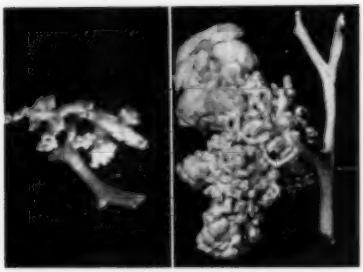


FIG. 37 (Left). Fragment of cast of normal lung showing distribution of terminal air passages. The terminal bronchiole and its branches are widely patent, with an actual increase in cross-sectional diameter in the region of the respiratory bronchioles. (× 4)

FIG. 38 (Right). Portion of cast of distal distribution of the respiratory passages in emphysema. Just beyond an irregularly narrowed bronchiole there is a labyrinth of air spaces greatly distended, presumably because of air-trapping. (× 2)

FIG. 39. Air-trapping abetted by a vicious cycle operating in bullous emphysema. As the bullae expand, adjacent bronchioles are stretched and suffer a reduction of lumen with a consequently greater tendency to air-trapping that results in further expansion of vesicles. Some of the bullae have been removed from the cast to demonstrate such an elongated and narrowed bronchus (arrow).

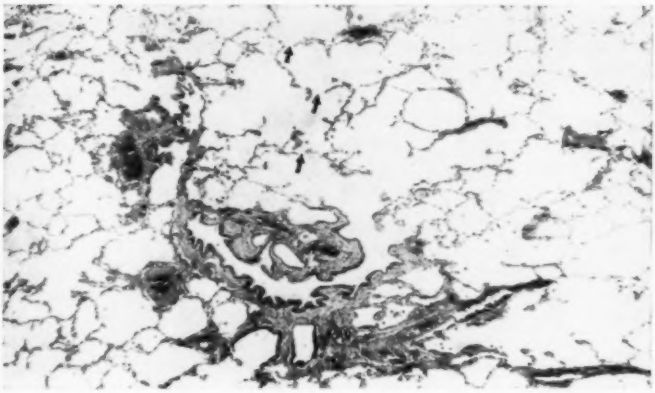


FIG. 40. Early emphysema beyond a thickened and narrowed bronchiole. Some air spaces are thickened, others are extremely thin with prominent lacunae (arrows). (× 30)

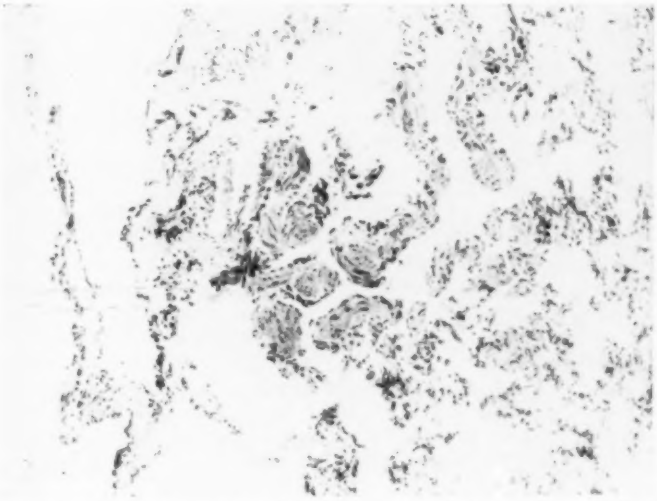


FIG. 41. Prominent "knobs" of smooth muscle in narrowed distal air spaces associated with emphysematous bullae. (× 100)

inspiration than with expiration. Resistance to air flow tends, therefore, even normally, to be greater during expiration. This effect is exaggerated if there is partial narrowing of bronchioles that becomes subtotal in that phase. In pulmonary emphysema, expiratory resistance may become extreme, as demonstrated by Fry and his associates (18). Such observations, however, provide no knowledge of the nature of the anatomic factors responsible for the obstruction. Obstruction, at least during inspiration, must, of course, be partial, since complete obstruction leads to atelectasis.

The obstruction of bronchioles may be episodic and brought on by accumulations of mucus, exudate, or by muscular spasm. Bronchitis, bronchiolitis, and pneumonitis frequently precede pulmonary emphysema and tend to recur in febrile episodes, whereupon evidence of respiratory obstruction tends to increase. In the acute necrotizing pneumonias of childhood and in postinfluenzal pneumonia, focal atelectasis and

emphysema are common. The former occurs when obstruction of bronchioles is complete. Acute pulmonary emphysema is the result of restriction of the lumina of bronchioles by exudate, sometimes with an actual valvular action. Many infections that appear to precede pulmonary emphysema are, however, clinically unspectacular, and dismissed as "bronchitis," although bronchiolitis and focal pneumonitis are probably the actual lesions of importance.

Much remains to be learned regarding the factors (including genetic) which govern the nature and especially the viscosity of mucus. Viscid mucus is competent to produce severe obstruction in bronchioles, as in "mucoviscidosis."

Smooth muscle in pulmonary emphysema is often notably increased in air passages as distal as alveolar ducts (figure 41), a position more peripheral than in asthma (24). The reasons for the evident hyperplasia and hypertrophy of this tissue are obscure. The beneficial effect of drugs that relax smooth muscle in some patients with emphysema suggests the possibility of spasm of the musculature as an air-trapping mechanism in some patients with emphysema.

McLean (4) has claimed that many bronchioles become completely obliterated in pulmonary emphysema, and that the alveoli beyond them are maintained in an overdistended state by air-trapping from adjacent distal air spaces as a result of collateral ventilation through the pores of Kohn. It can be demonstrated that the pores become enlarged when the lung is distended, since they are subjected to the same inspiratory traction as other structures in the lung. This can be shown experimentally by the ease with which smoke can be blown collaterally from one segment to the next when the lungs are distended in a vacuum jar after removal from the body (personal observation) in contrast to the difficulty encountered when they are allowed to collapse. Furthermore, while it is true that these pores can maintain the inflation of distal alveoli, the latter do not become overinflated. This is probably because the rate of inflow of gases by the collateral route is balanced by the absorbing capacity of the alveolar capillaries. As measured in a segment with an obstructed bronchus in the dog, it is not as much as 15 per cent of total inflow of gases were the bronchus patent (25, 26); in rabbits, collateral gas exchange is potentially greater (27).

This failure of distention in the presence of collateral respiration was demonstrated in the writer's laboratory by studies of lower lobes of patients with the common type of bronchiectasis, in which the basal segmental bronchi are, for the most part, blindly ending sacs, usually filled with mucus, in which the superior segment is, on the contrary, quite normal. The existence of the collateral ventilation was demonstrated by cannulating superior segmental and common basal bronchi separately and inflating the lungs in a vacuum jar. Collateral ventilation was demonstrated by the fact that the lung would not expand when the superior segmental bronchus was occluded. When this bronchus was left open, however, a wave of inflation along a straight, more or less horizontal, front passed downward from the superior segment collaterally through the pores of Kohn to envelop the basal segments. It is noteworthy that the alveoli surrounding the basal segmental bronchi, although open, are not overinflated in these specimens. While it is true that many minute bronchioles become obliterated in pulmonary emphysema, the usual fate of alveoli beyond such bronchioles is largely obliteration by scarring. This process contributes a force of traction as previously described.

During an acute phase of bronchiolitis, the pores of Kohn are likely to be closed, as they are whenever there is exudation, even of minor degree. Consequently, as mentioned, during the acute phase of necrotizing bronchiolitis, focal atelectasis accompanies focal emphysema consequent to partial obstruction of other bronchioles. The greatest inconsistency in the idea of air-trapping through the pores of Kohn as a distending mechanism is the fact that those distal air passages which are distended are often in direct free continuity with still-patent bronchioles. Thus, there is no need to assume the idea of a transalveolar method of air-trapping. Moreover, in later stages, large defects in interalveolar septa (to be discussed subsequently) freely connect adjacent alveoli, even those associated with other bronchioles.

The process of air-trapping may initiate a vicious cycle. An entrapped collection of air in the form of an intraparenchymal bulla acts more or less like a solid mass of tumor. This is true of the giant bullae that can form and which are competent to produce atelectasis and immobilization of the surrounding, relatively normal, pulmonary tissue. Air within such bullae can be

under supra-atmospheric pressure (28). Sometimes these giant bullae are sufficiently few and produce sufficient compression to make their surgical removal rewarding (*see* figure 29*E*). In addition, adjacent bronchioles or bronchi may become progressively elongated and flattened against the surface of the more or less spherical bulla (*see* figure 39). The greater traction during inspiration again tends to open these narrowed structures more widely during that phase. This process can, in turn, contribute to further air-trapping within the bullae or adjacent parenchyma, depending on the distribution of the bronchi.

A late obstructive mechanism may be related to the loss of tractional support of minute bronchioles, the result of a destructive process, the details of which are not exactly known (*see* below). Leopold and Gough (29) have described this very well in the common form of emphysema that appears to begin in a centrilobular position. As the respiratory bronchioles protrude into the complex, more or less bullous central chamber, little, if any, attachment to surrounding structures remains. These bronchioles have now lost the tractional support of the interalveolar septa, which formerly attached to, and exerted a pull upon, their walls from all sides. Inspiration proceeds relatively unimpeded but, during expiration, the walls of the unsupported bronchiole may be forced together like the flaps of a duckbill valve (figures 42 and 43). In their thoughtful discussion, Leopold and Gough (29) have indicated this possibility as "kinking." Such a valving mechanism is highly compatible with the air-trapping demonstrable functionally in some patients with late emphysema when asked to take a series of deep breaths in rapid succession with forced expirations, as pointed out by Dayman (30). If the common method of fixation by introducing the fixative into the major bronchi were employed, such an obstructive mechanism would be unapparent because the presumed valve would be fixed in the "open" position. This has been recognized by McLean (8). Obviously, it is desirable to compare lungs with this type of emphysema, not only upon fixation as if in maximal inspiration, but also in as close an approximation to its state during expiration as possible, i.e., maximally collapsed and then fixed by way of the blood vessels. A systematic study by this method is strongly indicated and may help to reconcile supposed inconsistencies between function and structure, particularly the observation of bronchi that are anatomically patent in the presence of clear functional evidence of air-trapping.

The fact that evidence of bronchostenosis is known to increase clinically during episodes of respiratory infection suggests the superimposition of additional, but often reversible, factors, such as accumulations of exudates and mucus, and bronchospasm. Again, the principle of potentiation of effects, some of which may be reversible, must be kept in mind.

Effects of air-trapping on distal air spaces: Attempts to produce air-trapping experimentally by introducing an expiratory obstruction or by other means have shown that it is difficult to produce permanent and irreversible overdistention of *normal* alveoli (31, 32). Hartroft (33) has cautioned against mistaking mere expansion of distal air spaces for "tearing" of alveoli. These efforts have, however, been directed against a large mass of pulmonary tissue, usually a lobe, or even more. Gough has also cited, as evidence against the pathogenetic role of obstruction, instances of asthma of extremely long duration without evidence of emphysema. It is obvious, however, that, under these circumstances, the degree of obstruction and air-trapping must be relatively slight when generalized or it could not long be survived. Focal overdistention may, however, be extreme, while the remainder of the lung is adequate to maintain function. Extreme overdistention, perhaps even of normal alveoli, may have destructive consequences to be discussed. With rapid distention, there may be the complications of interstitial emphysema and air embolism (22). It is possible, however, that slower distention will not lead to these complications but, rather, to atrophy and ultimate disappearance of interalveolar septa and even larger structures within the lung. When the distending force is exerted upon previously fibrotic alveoli, they will reach the largest size to which they can be stretched and will not return. Furthermore, retraction processes can occur simultaneously. Other destructive forces may also be at work.

Destruction

Although massive necrosis of lung tissue results in lung abscess and not in pulmonary emphysema, it is conceivable that necrosis may involve only parts of the walls of the alveoli, and thus lead to a solution of their continuity while stimulating

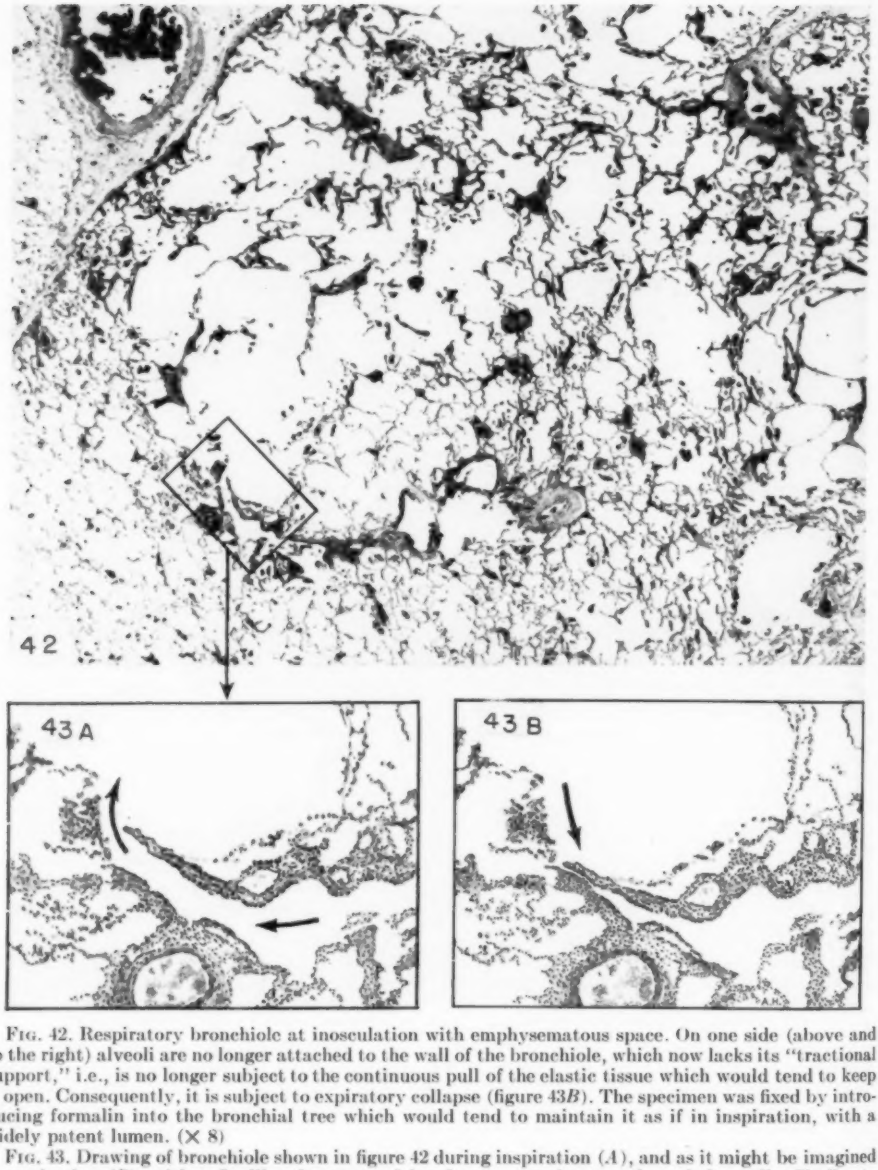
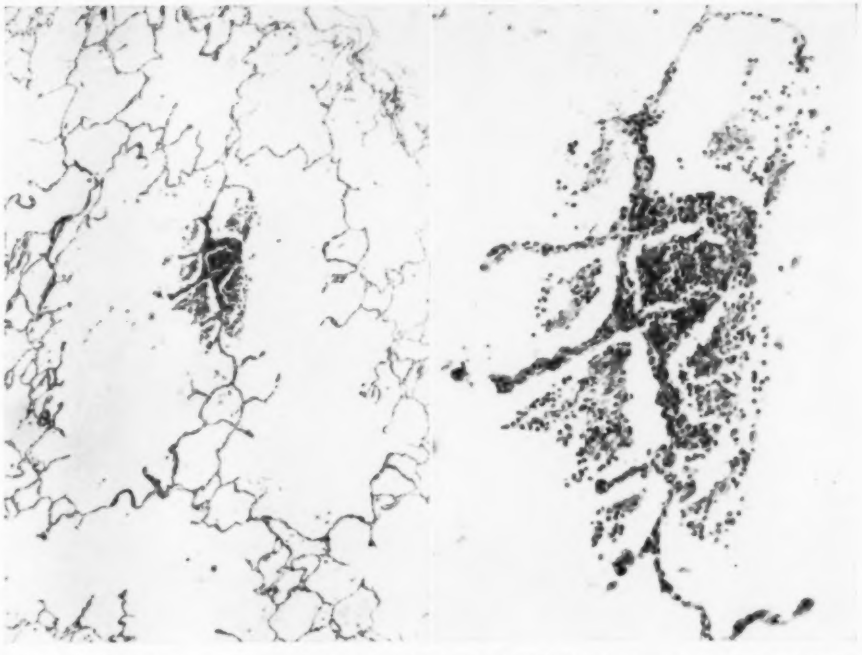


FIG. 42. Respiratory bronchiole at inosculation with emphysematous space. On one side (above and to the right) alveoli are no longer attached to the wall of the bronchiole, which now lacks its "tractional support," i.e., is no longer subject to the continuous pull of the elastic tissue which would tend to keep it open. Consequently, it is subject to expiratory collapse (figure 43*B*). The specimen was fixed by introducing formalin into the bronchial tree which would tend to maintain it as if in inspiration, with a widely patent lumen. (× 8)

FIG. 43. Drawing of bronchiole shown in figure 42 during inspiration (*A*), and as it might be imagined in expiration (*B*), with a flaplike closure resulting from a pressing together of the walls. Similar to figures 7 and 8 in Leopold and Gough (29).

fibrosis in other parts (figures 44 and 45). Such a process appears to take place within alveoli attached to bronchioles, especially respiratory bronchioles, in the presence of bronchiolitis. The lesions in the alveoli are best seen in the stage of organization, after exudate has largely been reabsorbed (figures 32 and 46). Under the circumstances, although the latter may fill some of the



FIGS. 44 and 45. Predominantly interstitial exudate and minutely focal necrosis in interalveolar septa In consequence of the necrosis there may subsequently be fragmentation of alveoli. The exudate within the alveoli may be eliminated without organization *in situ*. Newly formed fibrous connective tissue may ultimately thicken the walls of the alveoli as organization progresses. The ultimate state of these alveoli depends upon how much fibrous connective tissue is laid down in relation to the distending forces that may also be at work: It may contract, resulting in a pull on other portions of the normal parenchyma; or there may be retraction of fragmented walls of the alveoli. Tissue minimally fibrous may, however, be stretched, especially if there has been air-trapping. Figure 44 (× 30); figure 45 (× 100)

alveoli during the acute phases, it does not organize there.

Similar thickening and fragmentation affects alveoli attaching to respiratory bronchioles in "coal-miners' pneumoconiosis," as described by Heppleston (34) and, again, some of the distention may be in part a "traction" phenomenon.

Fibrous connective tissue that is thus laid down interstitially in the walls of these alveoli will have a tendency to contract, thereby producing traction or retraction; the latter may affect the residual spurs of fragmented alveoli. If the amount of connective tissue is minimal, yet sufficient to interfere with the "elasticity" of the alveolus, it may be distended by air-trapping or other forces, rather than be permitted to contract.

Certain features of pulmonary emphysema in its more advanced stages suggest a more subtle atrophy. These include: (*1*) the remarkably thin and often almost avascular appearance of many septa among the distal air spaces (figure 49); (*2*) the presence of lacunae or defects in the septa, as noted many years ago. Some observers, for example Sudsuki (35), have interpreted these as enlarged pores of Kohn while others, e.g., Orsós (36), have thought them to be newly formed "tears." Whatever the process, the interalveolar septa vanish and the process is progressive in that bronchioles and ultimately even bronchi come to communicate with a trabeculated, sometimes multilocular, and thin-walled cavity that may represent most of a lung (figures 47 and 48). Like the "Chambered Nautilus," it comes to consist of more and more stately mansions. The mode of dissolution of the interlobular septa is particularly obscure.

Certain mechanisms may be concerned in the

FIG. 46 (Upper). Destruction of interalveolar septa with formation of intercommunicating labyrinths of distal air spaces. The walls of some residual air spaces have been thickened by fibrosis; "retraction" also is in progress. (× 50)

FIG. 47 (Lower). Loss of interalveolar septa with confluence (arrows) of air spaces connected with two adjacent bronchioles, labeled *A* and *B* in the photograph. The residual walls of the distal air spaces are markedly thickened, as are the bronchioles. (× 30)

genesis of the atrophy:

Air-trapping: The possibility must be considered that air can be trapped in foci under sufficient pressure to compress the capillaries. This would tend to shunt blood into other vascular beds. If air is trapped under maximal deep inspiration and is not sufficiently rapidly absorbed, the pressure will be supra-atmospheric when the lung is allowed to become of any smaller size, especially during the expiratory phase (28). Supra-atmospheric pressure is also generated in the larger bronchi during cough if equilibrium is approached during the height of the cough, but if the trapped air is not freely vented during the subsequent expiration. It may be theorized that this is sometimes sufficient to exceed the capillary pressure, which varies between 8 and 2 mm. of mercury under normal circumstances. An approach to total cessation of blood flow must take place to affect the nourishment of the most distal air spaces. A *relative* decrease in perfusion, produced by im-

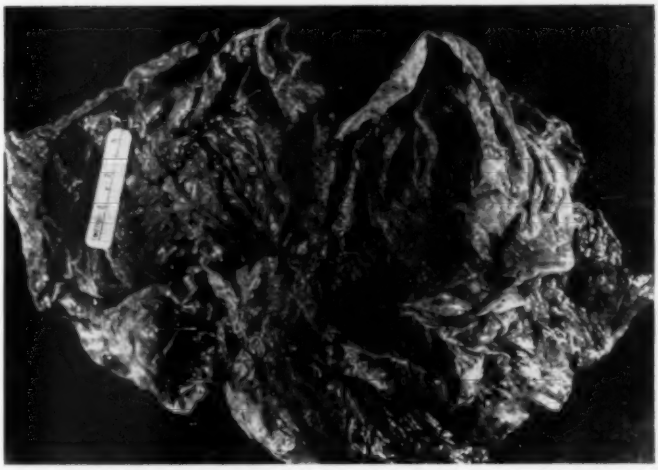


FIG. 48. Bullae shown in figure 36 after surgical removal. The entire upper lobe has been converted into a series of intercommunicating chambers crossed by remnants of largely obliterated vessels and bronchi. Others of these structures have been incorporated into the thickened wall. Immense numbers of interalveolar septa, bronchi, and vessels have been destroyed or obliterated, except for some which have retracted into the outer wall.

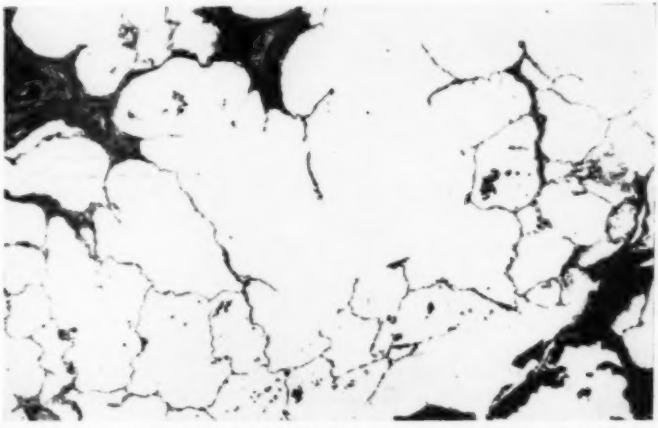


FIG. 49. Thinning and lacunar change in alveoli with compression and loss of capillaries. The walls of other alveoli have become thickened in continuity with perivascular and peribronchiolar scars. It is problematic whether capillary obliteration or the alveolar changes come first. The former appears more probable, and may be the consequence of air-trapping. (× 30)

mobilizing the lung, does not result in atrophy of the walls of the alveoli (37).

Poor aeration may also be associated with vasospasm (*see* subsequent discussion). It is inconceivable that this be total, however.

Another possibility is that vessels of distal air spaces may become occluded by thrombosis or some other mechanism beyond the range of the collateral vessels; normally, bronchial arteries do not extend beyond the respiratory bronchioles. It was observed before 1872 by Villemin (38) and by Isaaksohn (39), and was subsequently confirmed by Sudsuki (35) and Orsós (36) and others, that the vascularity of the alveoli is decreased in pulmonary emphysema. It is very uncertain, however, that the vascular changes precede the

atrophy. The theory that the vascular changes come first also does not explain the observation of relatively intact air spaces beyond the more expanded proximal portions, as described by Leopold and Gough (29), when it is recalled that pulmonary arteries are truly "end arteries"; involvement of such arteries should theoretically damage the entire lobule.

It has been theorized that obliteration of bronchial arterial supply can cause pulmonary emphysema (Cudkowicz and Armstrong (40)). This, however, is not supported by other observations of an expanded collateral arterial supply in pulmonary emphysema, especially in the presence of superimposed fibrosis and bronchiectasis (41, 42). Moreover, as has been noted, the bronchial arteries do not normally extend beyond the respiratory bronchioles in any event, and their loss could hardly account for disappearance of interalveolar septa. Furthermore, oxygen that reaches the pulmonary capillaries must first traverse the substance of the alveoli. For these reasons it would appear that loss of bronchial vessels is not the pathogenetic mechanism of pulmonary emphysema.

Loss of Elasticity

Certain evidence has been interpreted to indicate that the elasticity of the lung is reduced in pulmonary emphysema. Much has been written, but little proof has as yet been advanced that there is a truly *qualitative* change in the elastic substance of the lung in emphysema. It is true that the total tendency of the lung to collapse and, therefore, the inward pull on the thoracic cage, may be reduced in emphysema. This can, however, be the result of a quantitative, rather than qualitative, change in the sense that loss of alveoli means loss of the original total mass of elastic elements that are put on the stretch when the lung is made to fill a chamber larger than itself. Another factor is that each mass of trapped air, being, in a sense, a space-occupying lesion, tends to diminish the space that the remainder of the lung needs to occupy in the chest. The pull on the chest wall and other structures is thus diminished.

An additional and possibly important factor in loss of "elasticity" is interstitial scarring of the walls of the distal air spaces to a degree that makes it still possible for them to stretch but, being altered, to remain in a state of permanent distention. Consequently, the alveoli will reach the greatest size to which they are distended. The principle is that, while scar tissue tends to shrink, shrinkage in some circumstances may be counteracted by superior forces tending to distend the alveolus. It is even possible for some portions of scar tissue to yield to distention, while others of larger mass become contracted and thereby exert a force of external traction on the remainder of the parenchyma.

To postulate a reduction in the elastic *quality* of the lung tissue without fibrosis, as an effect of aging or other factors, seems superficially plausible, but fails to explain the lack of uniformity of the lesion, especially in its early phases. The development of an experimental method for producing such changes is still awaited. Striking emphysema is occasionally observed in young patients with Marfan's disease, a condition in which alterations in the elastic tissue of the aorta have been demonstrated.

Bronchiolitis in emphysema: While bronchiolitis is not the only lesion that is associated with emphysema, its importance is certainly great, as has been stressed especially by McLean (7, 8). It is apparent from preceding paragraphs that more than one mechanism contributing to the development of emphysema can be ascribed to bronchiolitis. A summarizing statement, although repetitious, may be in order as a description of factors in the evolution of at least one type of emphysema:

1. "Acute phase obstruction": air-trapping from valve-like accumulations of exudates and mucus (may reappear with recurrent bronchiolitis at any time)
2. "Interstitial alveolitis": focal necrosis with loss of substance of walls of distal air spaces and ultimate fibrosis of alveoli attaching to respiratory bronchioles, with variable consequences:
   a. "Tearing" of alveoli
   b. Traction and retraction phenomena
   c. Permanent stretching of fibrotic distal air spaces in the event that the distending forces exceed the force of contraction of the fibrous connective tissue
3. Late obstructive phenomena:
   a. Circumferential constrictive fibrous bronchiolitis
   b. Partial plugging by organized polypoid masses of exudate
   c. Muscular hyperplasia as far distally as respiratory bronchioles and even alveolar ducts, with possible obstruction from spasm
   d. Loss of tractional support of bronchioles in consequence of alveolar destruction (*see* 2*a* above), whereupon they function as expiratory flap valves.

The last is probably the most important in view of the prevalence of the centrilobular type of emphysema in which it occurs. Such obstruction mechanism may be especially effective when acting upon appropriately fibrotic alveoli (2*c* above); with extreme air-trapping of a focal type there may be compression of vessels with atrophy of tissue.

It is of interest that most of the phenomena mentioned as associated with bronchiolitis of presumably bacterial or viral etiology can also take place when the initiating agent is coal dust (34); it would be difficult to dismiss the possibility, however, that persons so affected do not manifest the effects of superimposed infections of the respiratory tract, especially bronchiolitis.

It is well to recall that the clinical level will not be attained until there is encroachment upon the large pulmonary reserve.

Vascular Changes

The total vascular cross-section of the lung must be considered in terms of the functional state of the vessels, as well as in terms of irreversible organic changes. The extent of the vascular reserve is indicated by the observation that, normally, at least a threefold increase in the output of the right ventricle can be tolerated without rise in pulmonary arterial pressure (13, 43). Several factors of either class acting in concert may exceed this reserve, while any single one may be insufficient to produce hypertension. This principle of summation or potentiation is too often forgotten.

In emphysema, pulmonary arterial hypertension is usually moderate, the mean pressure usually ranging between 15 and 37 mm. of mercury (44). Despite the moderate hypertension, the effect upon the right heart may be considerable. The relatively great importance of the functional factors is indicated by the reversibility of the pulmonary hypertension and its consequences upon appropriate treatment of many patients. This is in contrast to the irreversibility of hypertension associated with massive fibrosis, as in severe silicosis.

Functional Factors Affecting the Pulmonary Vessels in Emphysema

In patients with pulmonary emphysema, Harvey and associates (45) observed that, when the arterial blood did not become desaturated on exercise, there was usually no pulmonary hypertension. Yu and coworkers (46) found that the degree of the latter, in general, appeared to depend upon the severity of the hypoxia. West and associates (19) have stressed the significance of hypoxia in hypertension of pulmonary emphysema. Upon relief of bronchiolar obstruction, especially when this was produced by infection, and with restoration of compensation of the heart, both the pulmonary hypertension and congestive heart failure were gradually reversed as the alveolar oxygen tensions and systemic arterial oxygen saturations were restored to normal values (Harvey and associates (47)).

Spasm of vessels: Considerable evidence exists that reduction in oxygen tension in the alveoli can result in spasm of pulmonary arterioles. This has been demonstrated in isolated lungs by Nisell (48) and by Duke and Killick (49); in a single lung by means of bronchospirometric studies (Dirken and Heemstra (50), Peters and Roos (51)); in the entire pulmonary circulation of more or less intact animals by Lewis and Gorlin (52) and by Stroud and Rahn (53); and, in man, by McGuire, Westcott, and Fowler (54).

Increased blood viscosity: Hypoxia stimulates polycythemia, which increases the viscosity of the blood, a factor tending to contribute to hypertension in any vascular system. Polycythemia is not common in pulmonary emphysema except at high altitudes.

Blood flow: Another factor that affects pressure, other parameters remaining constant, is flow. Cardiac output may be increased in pulmonary emphysema (45). Some have ascribed this to the direct or indirect effects of chronic anoxia, including in this the expansion of blood volume associated with polycythemia.

Diminution in efficiency of blood-pumping action of respiratory movements: Another contributing factor is immobilization of portions of pulmonary tissue, whereby the blood-pumping action of the respiratory movements, as discussed earlier (*see* figure 28), fails in the affected parts. Such relative immobilization can take place when air is trapped or when there is sufficient fibrosis.

Compression of vessels: Compression of small vessels may occur temporarily or perhaps permanently in consequence of air-trapping, and this may lead ultimately to their obliteration and to atrophy of pulmonary tissue.

The problem of kyphoscoliosis: Cor pulmonale occurs commonly in kyphoscoliosis, although the mechanisms involved are not clear (55). There

appears to be no gross compression of pulmonary vessels because of the thoracic deformity (*see* figure 34). Contributory factors are immobilization of much of the lung tissue, especially the lower lobes. This results not only in diminished blood-pumping, but also in poor ventilation with hypoxia and, presumably, vasospasm in the affected tissue. In the overdistended upper lobes the initial "traction" emphysema may ultimately become obstructive and destructive, probably as a result of the frequent respiratory infections to which these patients are subject. The functional and organic consequences are similar to those in other types of emphysema except that the respiratory reserve is less because of the compressed state of so large a part of the pulmonary substance.

Organic Changes

The organic changes can reduce, but rarely in themselves exceed, the reserve of the vascular bed of the lung in emphysema. An accurate anatomic estimate of change in the total vascular cross-section of the lung offers a problem of almost insurmountable difficulty. Physiologic estimates are in effect means or even vector sums; the problem of the anatomist is compounded by the fact that pulmonary arteries are end-vessels in the sense that they do not serve as collaterals for one another. Consequently, a sufficient restriction at a single level can diminish inflow into a particular distribution without detectable anatomic changes above or below the restriction. An almost infinite number of levels must, consequently, be considered in attempting to reconstruct the total anatomic cross-section.

Granted that anatomic restriction has occurred, any superimposed physiologic factors tending to produce hypertension—for example, spasm of residual vessels—are the more likely to exert a significant effect.

Loss of capillaries: Loss of septa among distal air spaces, with ultimate confluence of increasing moieties of pulmonary substance, has already been considered (*see* figure 49). Whether the process is initiated by air-trapping or the result of atrophy otherwise induced, the effect is that the rich vascular beds vanish with the tissues that they once supplied. The loss of vascularity of alveoli in emphysema noted so many years ago is still not certainly explained.

Changes in larger vessels: The larger vessels formerly distributed to the capillary fields that have been obliterated reflect the changes by a remarkable muscular transformation. This may lead to their total obliteration (figures 50 and 51). They now persist as cords of largely muscular tissue and are either absorbed into the walls of bullae or continue to traverse their lumina. The lesion is somewhat analogous to the obliterative change that overtakes a systemic artery in which the distal vascular bed is abolished, as in amputation. The nature of the process in systemic vessels differs, however, in that fibrous and atheromatous changes, largely intimal in position, are dominant in reducing the lumen of the vessel. The stimulus to the *muscular* hyperplasia, specifically in these pulmonary vessels, is unknown (24).

Parker (56), in particular, has stressed the focal nature of these lesions, and has cautioned against a hasty decision that they are representative of the vasculature as a whole. The more spectacular lesions are all too likely to stimulate such erroneous conclusions. It must be asked whether these changes are causative of the emphysema or the consequence of the lesion. Most of the evidence points to the latter: First, occlusion of the pulmonary artery in a normal lung does not result in emphysema. Second, such muscular proliferation occurs in vessels often associated with tense projecting bullae, suggesting the role of air-trapping in previously obliterating the capillary bed.

Atheromatous and fibrosing pulmonary arterial changes are common in pulmonary emphysema. McKeown (57), in an extensive study of "pulmonary heart disease," stressed that these lesions must be considered against the background of arterial changes to be expected at the same age; Brenner (58), in particular, has shown the increase in prevalence of "sclerosis" of the pulmonary arteries with increasing years. McKeown's final statement is, "The most that can be concluded from this study is that emphysema accentuates slightly the normal age changes found in the pulmonary circulation." It is of interest that these changes bear no relationship to sclerosis of the aorta, coronary arteries, or other systemic vessels.

With reference to the smaller muscular vessels, there is a need for a quantitative re-study of this problem in correlation with an actual knowledge of the pulmonary arterial pressure during life.

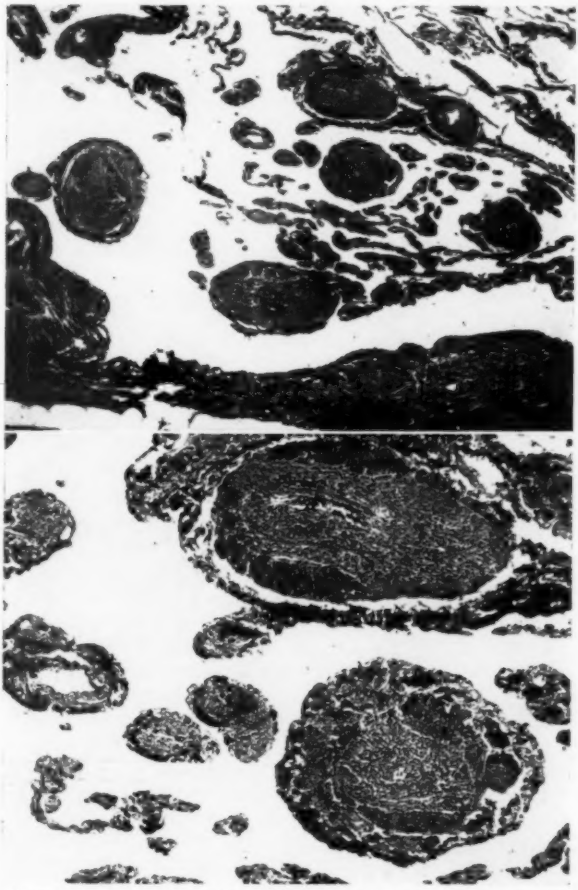


FIG. 50 (Upper). Vascular changes in bullous emphysema. The vessels are remarkably thick and, in some instances, narrowed to the point of obliteration. These vessels traverse or lie in the wall of a large bulla. These changes are focal and not necessarily indicative of diffuse pulmonary vascular disease. (× 40)

FIG. 51 (Lower). Same vessels shown in figure 50 at higher magnification. It is apparent that the thickening is largely the consequence of muscular hyperplasia and hypertrophy. The muscle is arranged in layers, which are longitudinal and chiefly intimal, and some are circular and occupy the position of the media. (× 150)

In the unusual cases in which pressure has been in excess of 50 mm. of mercury, the muscular walls of the arterioles generally may appear unduly thickened, although whether this is merely the anatomic indication of a spastic state or truly hyperplasia and hypertrophy of muscle is controversial. In the case of similar changes in mitral stenosis, Evans and Short (59), by careful measurement, concluded in favor of the latter. In other instances of severe pulmonary hypertension, as that which accompanies common ventricle, there is no doubt of the existence of both muscular hypertrophy and hyperplasia of the arterioles of the lung. In such conditions, this change appears clearly to represent the effect, rather than the cause, of the hypertension, and it may be truly the anatomic expression of increased tonus long maintained. Here the

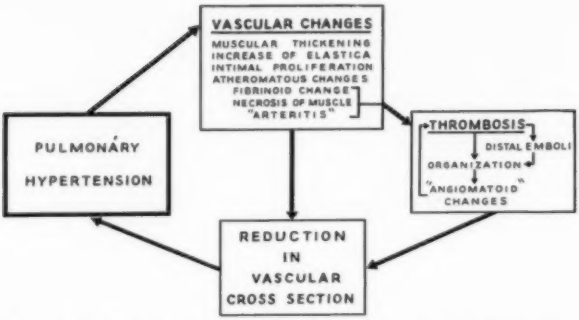


FIG. 52. Schema of possible effects of severe pulmonary hypertension in inducing damage to pulmonary vessels. The damage results in restrictive changes, frequently with further reduction of the vascular cross-section, whereupon maintenance or increase of hypertension is favored. The vicious cycle is only rarely operative in pulmonary emphysema in which the hypertension is usually not severe.

pulmonary vessels have been subjected to systemic pressures and torrential blood flows. The occurrence of necrotizing arterial lesions and pulmonary arteritis and "periarteritis," as seen in extreme pulmonary hypertension of various other causations, must be extremely rare in pulmonary emphysema. A graphic representation of the most likely sequence of events in these states is given in figure 52. It must be emphasized that this schema has only limited relevance in the relatively mild hypertension associated with most cases of pulmonary emphysema.

It has been stressed by some that the focal vasorestrictive changes are associated with thrombosis or embolization in pulmonary emphysema. Thromboembolism doubtless is favored by polycythemia when it exists. Severe atherosclerotic lesions of the large pulmonary arteries may ulcerate, become the seat of thrombosis, and emboli may thence seed peripheral vascular beds. This is rare in emphysema. Kernen and his co-workers (60) found that "pulmonary arteriosclerosis" as seen in emphysema was not correlated with right ventricular hypertrophy (used as an indication of the existence of hypertension), but rather with thromboembolism.

Collateral arterial supply: The collateral arterial blood supply has been mentioned briefly in relation to the theories of the pathogenesis of pulmonary emphysema. Briefly, it may be said that it appears not to be involved in the causation of the emphysema, nor otherwise, except insofar as it expands in relation to the severity of associated fibrosis, bronchial disease and, especially, bronchiectasis. The hemodynamic effects can only be briefly discussed since they have little, if any, importance in emphysema in the "pure" form.

In the presence of complicating conditions, especially bronchiectasis, the bronchial arteries not only tend to approach in size the pulmonary arteries at the same level, but also anastomose freely with them (61, 62). In experimentally induced pneumonia (63) or after interruption of the pulmonary artery, the bronchial arterial collaterals expand with great speed (33). From the pressure differences at the sources, it might be expected that blood flow would be from the bronchial to the pulmonary vessels. The actual pressure relationships have not been measured, however, and can only be inferred. Evidence that blood is shunted away from points of anastomosis in the diseased tissue to normal pulmonary substance capable of gas exchange is the absence of systemic arterial desaturation when even as much as a whole lung is involved in conditions such as bronchiectasis or tuberculosis (64). It is obvious, then, that these anastomoses may be points of increased resistance to outflow from the right ventricle. This factor must be considered, however, in relationship to the expansible reserve of the pulmonary vascular bed.

Reversal of blood flow against the usual direction of the stream in the pulmonary artery has been demonstrated in massive bronchiectasis, first in 1949 (64), and again more recently (65). In the latter instance the reversal was demonstrated angiographically by retrograde filling of the pulmonary artery when the contrast medium was introduced into the aorta above the origins

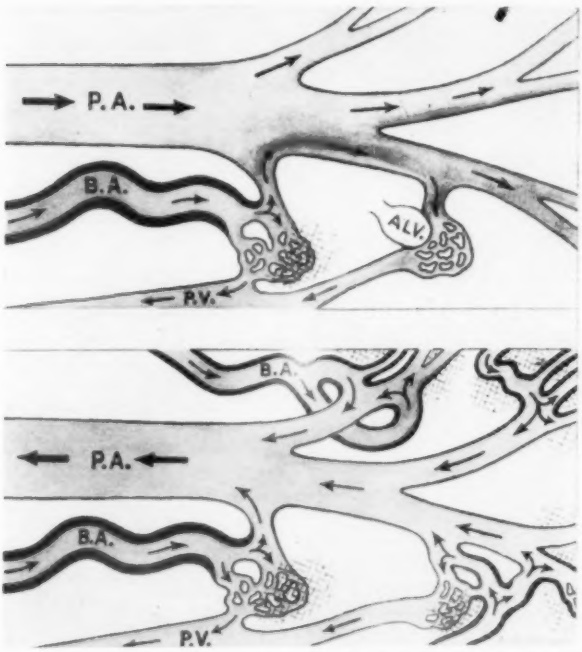
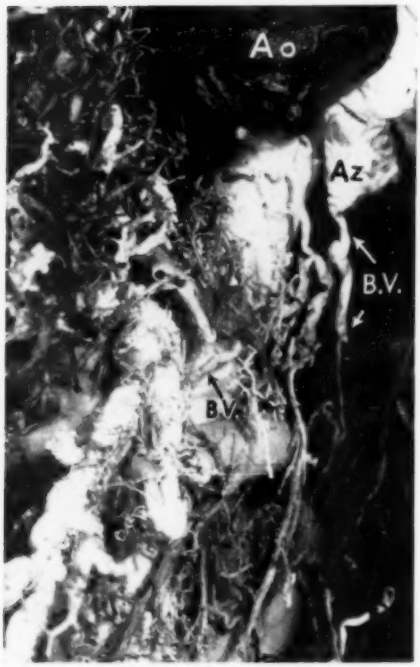


FIG. 53. Diagrams of reverse flow in pulmonary arteries via bronchopulmonary anastomoses in chronic disease of the lung. Partly obliterated capillary beds are indicated by cross-hatching. In regions of fibrosis there may also be some newly formed capillaries derived from expanded bronchial arteries. Communications of the latter are shown by means of precapillary anastomoses with branches of the pulmonary artery which they tend to approach in size at the level of anastomosis. The presumed direction of blood flow is indicated by arrows. In the upper figure, blood flow is reversed only in the single small branch of the pulmonary artery that is in anastomosis with one bronchial vessel in a localized region of scarring. In the lower figure, in which numerous anastomoses are present, blood flow is reversed in a major pulmonary artery. This phenomenon has been demonstrated for an entire lung universally involved in bronchiectasis (64, 65).

of the bronchial vessels through which it entered the lung. Similar, but localized, reversal of blood flow is suggested by the observations of Roosenburg and Deenstra (66), but these are somewhat questionable on the grounds of the difficult technical problems involved. A theoretic schema that indicates the possibility of local reversal and of reversal within a larger system of pulmonary arteries in the presence of more numerous anastomoses is shown in figure 53. A factor favoring this reversal of flow, doubtless, is the presence of scarring with diminution of the original pulmonary capillary bed.

Collateral venous drainage: Of greater interest than the arterial is the venous side of the collateral circulation in emphysema, which appears to be expanded far beyond what is observed in other types of pulmonary disease (41, 42). This is not simply an expression of the generalized congestion of systemic veins associated with failure of the right heart, since it exists in the absence of failure. Furthermore, in severe mitral stenosis, the dilated "bronchial veins" that have been demonstrated in this condition are predominantly branches of the pulmonary veins and not the "true" bronchial veins that join the systemic venous drainage (67).

Normally, the "true" bronchial veins connect freely at one end with the large hilar pulmonary veins and, at the other, join plexuses of mediastinal vessels that lead to the azygos venous system, superior vena cava, and ultimately the right heart (41, 42, 68). That blood flow in this system is toward the right heart is deduced from



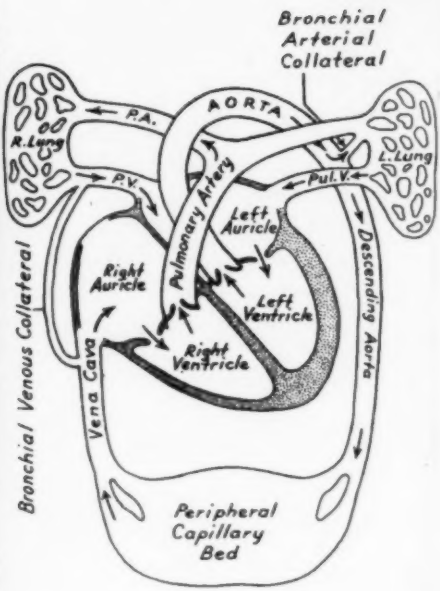


FIG. 54 (Left). Collateral venous system in pulmonary emphysema. Bronchopulmonary venules connected with branches of the pulmonary veins and intimately applied in a rete to bronchi in the superior segment of the left lower lobe are clearly visible in large size to the fifth-order bronchial branches; proximally they are in continuity with bronchial venules (*B. V.*) and these proceed into a mediastinal plexus which enters the azygos vein (*Az*). The aorta (*Ao*) has been transected to expose the mediastinal structures.

FIG. 55 (Right). The bronchial venous collateral system is indicated as a bridge between the systemic and pulmonary veins. This bridge is expanded in pulmonary emphysema to the extent that the valves within the true bronchial veins become incompetent, whereupon blood can flow in either direction. With failure of the right heart associated with pulmonary emphysema, the pressure in the right atrium can come to exceed that in the pulmonary veins, whereupon the direction of flow would be from the right to the left side of the heart, the opposite of the normal. Such a shunt represents an extrapulmonary contribution of desaturated and hypercapneic blood to the left atrium and systemic arterial circulation.

the facts that the mean venous pressure is slightly higher in the left atrium than in the right and that the valves in the bronchial veins point toward the azygos venous system. Rapid expansion of collateral venous drainage can be induced experimentally (69, 70).

In advanced emphysema, whether or not there is congestive heart failure, the bronchial veins become remarkably expanded and can be traced along the bronchi to the sixth order branches and beyond (figure 54). As the diameters of the bronchial veins double or more than double the valves become incompetent, whereupon blood is free to flow in either direction. When cardiac failure supervenes in the *cor pulmonale* associated with severe pulmonary emphysema, the pressure in the right atrium may come to exceed that in the left, whereupon desaturated blood from the mediastinal plexus will flow in reverse of the usual direction—to the pulmonary veins. Thus, there is a contribution terminally to hypoxia and hypercapnia by a more or less extrapulmonary shunt (figure 55).

With the development of a notable collateral circulation involving the azygos venous system in chronic hepatic disease, a similar shunting of

desaturated blood into the pulmonary veins has been postulated (71) and, in one instance, demonstrated angiographically (72).

Summary and Conclusions

An analysis of both anatomic and physiologic evidence suggests the futility of seeking for a single etiology and pathogenesis of emphysema. The disease appears to be the result of a combination of several factors. Among these, the dominant appear to be the destruction of pulmonary tissue and obstruction of distal air passages. These two are inter-related and the one may contribute to the development of the other. Obstruction may be early and associated with edema, excessive mucus production, or exudate in the bronchi; or it may be late and associated with rigid or valvelike obstructive mechanisms. Loss of traction upon bronchioles when supporting alveoli are destroyed is probably an important mechanism. Furthermore, phenomena of traction and retraction resulting from scarring in obliterated small distal masses of pulmonary substance, or interstitially, can contribute to the enlargement of residual distal air spaces. It is also possible that the elastic quality of pulmonary substance can be changed, but this possibility in particular requires much further study. It may be occasioned by a minimal degree of interstitial fibrosis of alveoli that causes any overdistension to be permanent.

Most of these pathogenetic factors are often associated with repeated episodes of necrotizing bronchiolitis and pneumonitis, both intra-alveolar and interstitial, but chemical agents and certain dusts can produce similar effects. Infections are often superimposed upon pneumoconiosis.

Vascular changes are occasioned by both functional and organic factors, and these supplement each other. The former seem more significant, as judged by the reversibility upon appropriate treatment of the mild pulmonary hypertension associated with emphysema. Irreversible organic changes in the vasculature, however, reduce the large reserve of the lung, whereupon the effects of hypoxia (which may include pulmonary vasospasm and left ventricular failure) become manifest. The most important vascular lesion appears to be a loss of capillaries. Lesions of the larger arteries which include muscular hyperplasia and sclerotic changes are often focal and are, in part, associated with this diminution in the peripheral capillary bed. The latter may, in part, also be the result of thromboembolic phenomena which occur commonly in pulmonary emphysema. Only in rare instances does death from fixed decrease of total vascular cross-section occur. As a corollary, it may be said that such changes as appear to be induced by very high levels of pressure in the pulmonary arteries occur very uncommonly in pulmonary emphysema.

The arterial collateral circulation is significant neither in the causation of pulmonary emphysema nor in altering the hemodynamics unless there are superimposed extensive fibrosis, bronchitis, and bronchiectasis. The venous collateral circulation, however, is often notably expanded in emphysema and, when the right heart fails, it provides the possibility of shunting of blood from the systemic into the pulmonary veins. Thus, an additional contribution to anoxia and hypercapnia may exist in the late stages of pulmonary emphysema. Quantitative studies of the anatomy of the lung in such a condition as emphysema are of immense difficulty. The true pathology of this disease is only partly revealed.

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General Discussion

Dr. Fishman: As the assigned discussant, I am happy that Dr. Liebow has extended his remarks beyond the pulmonary vascular changes of emphysema, for there is little to say about these vascular changes. Anatomists are generally agreed that the systemic arterial blood supply to the lung undergoes little proliferation, except possibly in the vicinity of bullae. They are also in accord that the capillary bed is attenuated, and Dr. Liebow has demonstrated the amazing expansion of the venous part of the pulmonary vascular tree. But, as far as functional significance is concerned, we are on surest ground with the capillary bed since there is ample physiologic evidence that curtailment of this bed limits the gas-exchanging surface of the lung in emphysema.

With respect to the more general aspects of emphysema, Dr. Liebow has stressed that postmortem examinations may overlook functional alterations, such as bronchial plugs and spasm of smooth muscle in bronchi and vessels. He has also recognized that the terminal manifestations of lung disease may obscure initiating mechanisms. But, he has not indicated whether the anatomic approach to emphysema by way of tissue fragments and injection is sufficient to provide a basis for clinical and physiologic understanding of emphysema.

It is true that this approach has been extremely revealing in clinical states such as bronchiectasis, and experimental states such as ligation of a pulmonary artery; these alter the vascular supply to the lung in a large and characteristic fashion. But, one may question the attempt to *recreate* the performance of a lung on the basis of a tissue fragment or an injected lung specimen. As a nonpathologist, one could suppose that it would be more rewarding to *measure* the performance by clinical and physiologic methods in human subjects prior to death and correlate the results of these *in vivo* studies with the findings at autopsy.

Such an approach has been proposed by Gough, based on large sections of the lung. The value of such sections was appreciated by Mathew Baillie, whose book reproduces a large section of the emphysematous lung of Samuel Johnson, the lexicographer. Unfortunately, Johnson's clinical course was depicted by literary men rather than physicians, and physiologic measurements were not available in 1870. Consequently, a good clinical-physiologic-anatomic correlation is not available.

It is exciting to witness the excursions of the pathologist into physiology to gain support for an hypothesis suggested by morbid anatomy. Nonetheless, it must be recognized that the result is often comparable to a lawyer's brief, with marshaling of evidence to support a particular case. This objection may be directed against the references to "vascular spasm" in hypoxia. The evidence for "spasm" derives from a curious mixture of acute and chronic experiments, diverse inspired oxygen tensions, and a variety of animal preparations. The results of these experiments have not always been consistent and a strong argument can still be made for mechanical factors rather than vasomotricity as bases for pulmonary hypertension in the intact human suffering from emphysema. But rather than enter into such a discussion, I would prefer to ask if any pulmonary vessels in emphysema develop muscular coats which can respond to physiologic stimuli so as to appreciably affect the resistance to blood flow. What is meant, in anatomic terms, by "restricted vascular bed"? What is the anatomic expression of a chronically augmented central blood volume?

Dr. Liebow has considered many types of emphysema. In so doing he has performed a valuable service on many counts. To me, his most valuable contribution has been the emphasis on the wide variety of diseases which masquerade under the term "emphysema" and, as a corollary, the need for definition and clarification: definition, so that we can communicate at meetings such as this and in published reports; classification, not to partition our ignorance, but to sort diverse diseases into patterns for study.

In this light, it is pertinent to recall that "emphysema" represents an anatomic end to many different pathogenetic processes. This common final picture is related to the fact that the lung parenchyma, comprised of vascular septa under stress and strain, has only a limited capacity to respond to these distorting forces. The usual response is one of overdistention of individual units to the point of tearing and disruption. One possible initiating mechanism, referred to by Dr. Liebow, i.e., bronchiolar obstruction, is commonly identified with emphysema. But, bronchiolar obstruction is not an inevitable antecedent of emphysema. Dr. Laurenzi, at the last meeting of the National Tuberculosis Association, reviewed our experience with a group of patients who were found to have freely communicating, bilateral, pulmonary air cysts. He displayed the lungs of a patient with Marfan's disease to illustrate this type of lesion and raised the question of abiotrophy, rather than bronchitis, in the pathogenesis of certain types of emphysema. With respect to the "emphysema" of kyphoscoliosis, the experience of Dr. Bergofsky in our laboratory would suggest that this is merely a distorted lung, adjusting to its space as does an "aging lung" or the remaining lung after pneumonectomy. In this case, the term "emphysema" is misleading if it

implies the nonhomogeneity of ventilation and perfusion which characterizes the "emphysema" of chronic bronchitis.

I have avoided any detailed consideration of the physiologic mechanisms proposed by Dr. Liebow. However, I should like to voice some reserve concerning his representation of the effects of inspiration on vascular size and filling. I believe that to reproduce his model, a particular anatomy would have to be established which would include radial insertion of elastic fibers onto the vessel walls. I do not know that this occurs in normal lungs, let alone lungs altered by disease. Moreover, with respect to the effect of inspiration on the pulmonary capillaries, I should only like to indicate that there is little accord among physiologists on conditions which potentiate filling or emptying of these vessels during respiration.

In closing, I should like to thank Dr. Liebow for his provocative presentation. He has provided the conference with much basis for thought and discussion.

DR. MITCHELL: Could anyone tell us what senile emphysema might be?

DR. DAYMAN: Senile emphysema is not a disease of the lungs at all but a misshapen contour of the thorax.

DR. PIERCE: Dr. Ebert and I studied pulmonary functions on a group of patients who had marked barrel deformities of the chest and compared these with 15 unselected patients more than sixty-five years old who were admitted in succession for prostatectomy, and we could find no detectable difference in these groups. If there is such a thing as senile emphysema, it is entirely different from pulmonary emphysema as usually described.

DR. BRANTIGAN: Dr. Liebow has shown that in emphysema, as well as in bronchiectasis and mitral stenosis, the bronchial arteries are dilated. In a series of 35 patients upon whom I have stripped the pulmonary hilum of all tissue except the pulmonary artery, pulmonary vein, and bronchus, I have not noted dilated bronchial veins, suggesting that the bronchial arterial runoff is into bronchial venules, which in turn drain into the pulmonary veins.

MACROSECTION AND INJECTION STUDIES OF EMPHYSEMA[1]

JOHN P. WYATT

Introduction

Before presenting some of our findings on the macrosection technique as a quantitative tool to study emphysema, I feel that I must comment on the discussions that have been given by the three pathologists earlier this afternoon. Dr. McLean has shown with his admirable studies on pathogenesis of emphysema that he has been reading from the book of Genesis. For the moment I was at a loss, judging from the antithetical theme of the remarks directed by Dr. Berthrong against Dr. McLean's paper, but it does remind one of the writings of Emile Zola in his famous letter "J'accuse." From Dr. Liebow's investigations into the bronchial and vascular pathways, he has been reading from the book of Revelations. Earlier this afternoon several of the functionalists jumped up, one from Boston in particular, and referred to the reluctance of the pathologists in that area to quantitate the emphysematous lesion in the lung, and this touches upon my Apologia of this afternoon. My remarks are drawn from the Confessional Prayer Book. Frankly, I would be remiss if I didn't openly admit that I had been goaded and shamed by the functionalists into studying emphysema by "quantitative" morphologic methods. But I must also remind the functionalists in the audience that the principal reason for this is that they want something to take away with them to impress their confreres at the next convention!

We adapted the large lung section, which was originally introduced by Gough. This technique is mandatory if there is an active pulmonary function laboratory keeping the hospital full of emphysematous patients. An active pulmonary function laboratory dictates also that a number of the clinical-pathologic conferences held during the school year will feature emphysema. The pathologist's "side" is greatly weakened if he only has a single tortured 3- by 1-inch slide to comment upon when the respiratory physiologist has been working for weeks on a bewildering array of functional alterations. All of this may be summarized by saying that in emphysema the lung is stuffed with air so that the functionalist has a whole lot of nothing doing something, and the pathologist with a single section has a little bit of something doing nothing! The large lung section is the ideal technique to solve this dilemma.

Method

This afternoon I would like to show the macroscopic anatomy of the emphysematous lung using the whole lung slice technique. We have used this technique in 275 cases, a large number of them revealing the alterations of emphysema.

Our modification from the original technique, as laid down by Gough of the Welsh National School of Medicine, is that prior to full inflation of the respiratory tree with formalin we inject the artery and vein with colored latex and then harden the lung in a formalin bath. A few days later, 1-inch sections are cut and embedded under vacuum with gelatin. Whole lung slices at 200 to 300 micra are mounted on thin translucent paper, and multiple paper sections are prepared. By this technique one can give the pulmonary functionalist something to take away in his briefcase, and he goes through life a contented man.

Figure 56 shows the 1-inch slice of lung previously injected with colored latex (yellow in this case) into the pulmonary artery and with the entire respiratory tree insufflated with 10 per cent formalin. The solid gelatin block is easily mounted on a warm microtome stage measuring about 9 by 11 inches. Many sections can be cut from a single lung specimen. This first specimen is actually of a "honeycomb lung," in my opinion, better-labeled primary fibrosing cystic bronchiolectasia. This illustration clearly outlines the tremendous value of the macrosection.

A classification of emphysema has been suggested by Dr. Liebow. I'd like to refer to several variants this afternoon. The first type that Dr. Liebow referred to he classified as "tractional emphysema." We have been referring to this as paracicatricial and believe that it is primarily the enclavement of air spaces in the lung by radiating bands of fibrous scar (figure 57). In essence it is not an illustration of genuine emphysema, nor is it "compensatory" in nature. We prefer to look upon this as a paracicatricial air cyst formation and in

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FIG. 56. Macrosection of "honeycomb" lung.

relationship to any scar. The scar may be due to silica, obsolescent tuberculous infection, old infarct, or areas of atelectasis distorting lobules.

A second type of emphysema which has come into relief by use of the large lung section is a diffuse form which probably is best labeled centrilobular emphysema. The lobule which we are referring to here is based upon Miller's concept of the *secondary* respiratory lobule of the lung. Briefly, the secondary lobule of Miller consists of five to a dozen terminal bronchioles and their related primary respiratory units encased in a connective tissue framework which runs out from the hilus to the periphery. The secondary lobules are very clearly demonstrated with the large lung section technique. The earliest beginnings of this form of emphysema appear to be at the site of the terminal bronchioles, where they are noted to be anatomically centrally situated in the secondary lobule of the lung. A higher power of the paper section is shown in figure 58. Distention and break-up of the terminal bronchiole is noted in this figure to be closely associated with the surrounding distended air sacs; the entire grouping forms a confluent pool of air. This form of centrilobular emphysema may be concentrated in one or two secondary lobules, with remaining portion of the lung free of the alteration, or it may be a diffuse and advanced type throughout the lung field.

The next type of emphysema, which made up about 8 per cent of our total group, is the type we are speaking of as segmental emphysema. Usually this type of segmental emphysema is concentrated at the apex, as may be seen in the large lung section. The black lines on this large lung section (figure 59) indicate what might well be considered as outlines of the excisional peripheries of the disease, which certainly pleases the surgeon as it implies a surgical procedure for a medical condition! Actually, this is probably unsound because, on closer examination of the whole lung section, it is usually easy to demonstrate emphysema in other areas of the lung. It does, however, suggest that segmental emphysema may have its beginnings in a centrilobular situation, and aggravation and extension of the condition may be due to interference with collateral air flow. The apical segmental group in which the accentuated bullous fields are noted, particularly in the younger age groups between forty and fifty, in some instances has been traced back to a partial stenosis of a major bronchus.

Another form of emphysema, which we prefer to label the multicameral bullous cyst, probably represents an extravagant form of segmental emphysema. The fibrous tissue septa which separate the bullae contain latex and clearly indicate that the inner walls of the bullous cyst are attributable to the blood vessel scaffold. In both the apical seg-

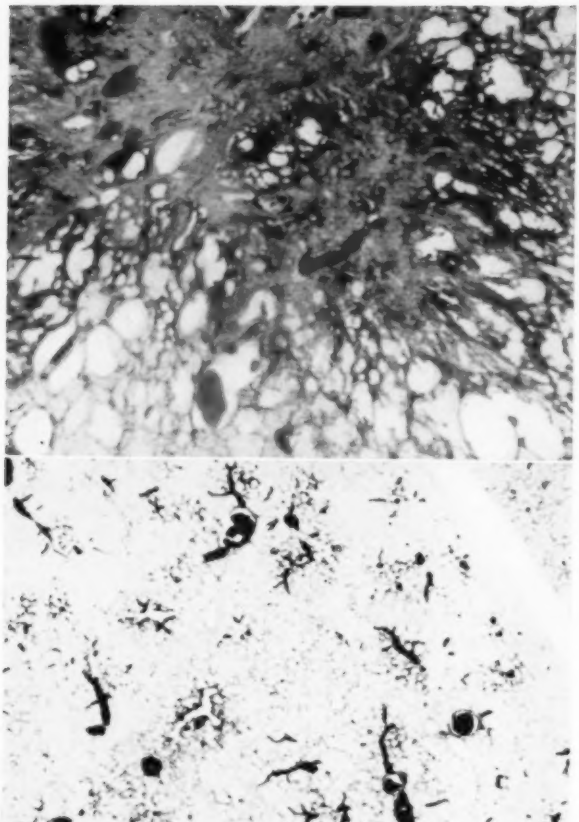

FIG. 57 (Upper). Paracicatricial "emphysema" or air cyst formation.
FIG. 58. (Lower). Centrilobular emphysema in secondary lobule (high power of paper section).

mental group and the multicameral bullous cyst there is evidence in other parts of the lung of the beginnings of centrilobular emphysema.

I would like to turn, for the moment, to another form of centrilobular emphysema which has been drawn from the southern Illinois soft-coal fields. Any remarks which I make on coal and its etiologic role in emphysema I would prefer not to be quoted on at this time, as it would bring me into direct conflict, not only with John L. Lewis, but with the insurance company which has the mortgage on my house!

Some years ago a re-evaluation of the coal and its etiologic role in pneumoconiosis came about principally due to the efforts of a research group at the Welsh National School of Medicine. The effects of coal upon the lung investigated by the macro map of the lung in coal workers in the United States has not been previously used except in one or two instances by Heppleston. We have observed coal-workers' pneumoconiosis in nine instances now. All of the workers have been working and mining underground in the soft-coal fields. From Gough's work on the coal-workers' lung, coal has been incriminated as the dominant causative factor in the production of a generalized emphysema.

In figure 60 the early stage of coal-workers'

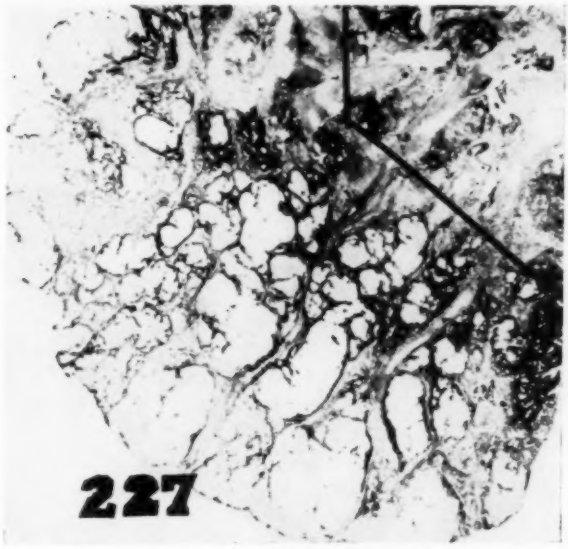

FIG. 59. Localized segmental emphysema at lung apex.

pneumoconiosis, which we may speak of as stage I, is revealed, with the soot or carbon concentrated around the centrilobular supplying bronchioles. Examination of the nature of the emphysema reveals that the beginning and even the advanced stages of coal-workers' emphysema remain confined to the centrilobular areas. Dilatation of the surrounding air sac units is noted, as well as the irregular outline of the distended supplying bronchiole, the combination of the two producing a confluent air pool. In the next section a blow-up of the same area is shown, and these foci of confluent air pools and the mantle of coal pigment are clearly demonstrated. Silica has no etiologic role in coal-workers' pneumoconiosis. The major reason for showing the centrilobular emphysema that develops in the coal worker is to indicate that the identical anatomic site is noted in many cases of nonindustrial emphysema. I am using the industrial emphysema produced by coal as a framework to emphasize that nonindustrial emphysema in the middle-aged male has its beginnings within the centrilobular situation and in this respect is similar to coal-workers' emphysema.

In figures 61–63 the advancement of the centrilobular emphysema may be noted, continuing until large, punched-out cystic areas are produced in the lung. These illustrations have been taken from a number of miners in the southern Illinois coal fields and we have come to think, as Gough has shown previously, that the coal macule is an indelible and an invaluable mark of an occupational history (figure 61), particularly of the soft-coal-mining fields. We have on occasion, of course, noted the soft-coal macule in the lungs of persons occupied in the dusty atmospheres in St. Louis, but the numbers of large macules and the close communion of focal emphysema such as we have observed in the soft-coal worker has not been found. Figures 62 and 63 illustrate lung lesions in miners from the coal fields of southern Illinois. One can see a scattering of coal macules; but the outstanding feature is that the degree and extent of emphysema far outstrip the markings of the coal. This brings up the question, of course, of whether or not the beginnings of coal-workers' pneumoconiosis followed by an extensive degree of generalized emphysema may represent the pathologic liability of nonindustrial emphysema which is seen in the middle-aged male (figure 62). Emphysema in the coal worker is not necessarily coal-workers' emphysema! One of the large lung sections is from a miner who worked twenty-nine years in the southern Illinois coal fields as an underground worker. The apical scar may be

FIG. 60. Macrosection of coal-workers' pneumoconiosis showing centrilobular emphysema.

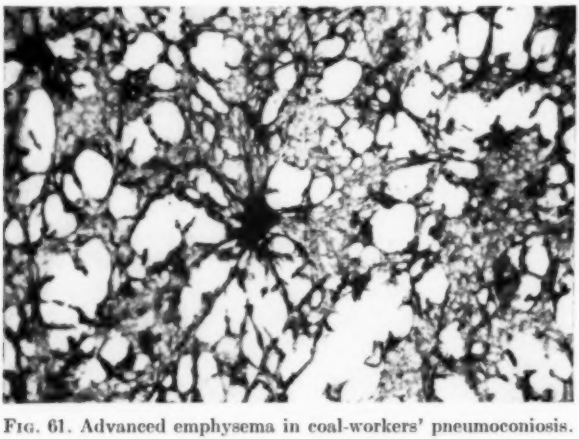

FIG. 61. Advanced emphysema in coal-workers' pneumoconiosis.

noted with the association of paratractional air cysts around these scars and a black pigmentation. Throughout the lung, the marked accentuation of bullous fields is revealed. Only in the occasional area is the occupational mark of a soft-coal-mining activity recorded by the morphologic evidence of coal macules (figure 63). Here we have an instance in which there is a mod-

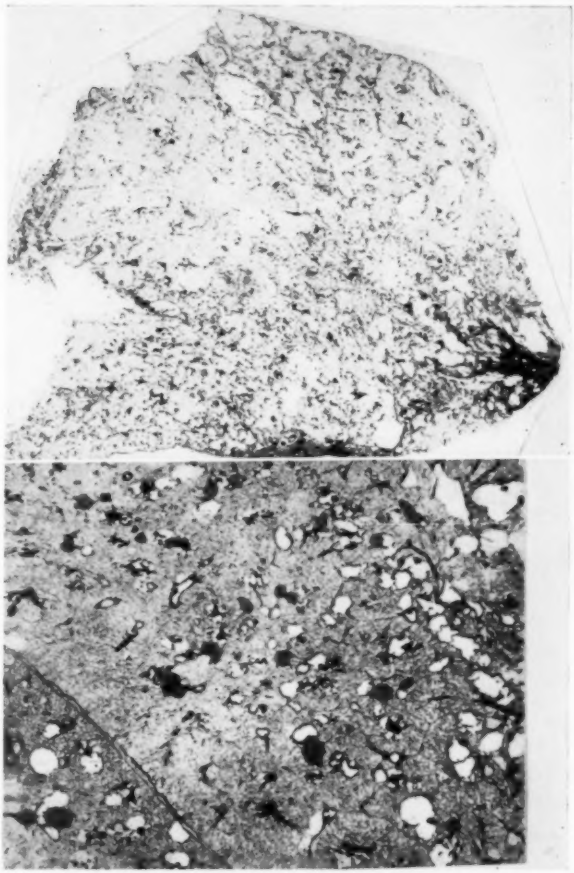

FIG. 62 (Upper). Emphysema in a coal worker with only minimal and probably unrelated coal-workers' pneumoconiosis.

FIG. 63 (Lower). Same as figure 62, higher power showing isolated coal macules.

est degree of coal-workers' pneumoconiosis, but with a well-established dissolutive form of anatomic emphysema. Usually in coal-workers' pneumoconiosis the nodule and the emphysema form a communal lesion, coequal in distribution and extent; in this particular case the emphysema has far outstripped the markings of industry.

The next group of figures depicts pulmonary alteration in civilians in St. Louis, many of whom have had pulmonary function studies. The outstanding feature throughout all of these is the development of centrilobular emphysema with progression in some of the cases to the development of accentuated bullous fields and, in one or two instances, the conversion of half of the lung into extremely large bullous areas. The morphologic implication of these findings is that the centrilobular emphysema represents the beginnings and that the bullous fields, because of the punched-out-outline and retention of their peripheral fibrous tissue skeleton, indicate that they are the end phases of centrilobular emphysema (figure 64). In some of the large lung sections the breaking up of the centrilobular lesion is seen, the dilated terminal bronchioles coming into association with the outer portions of the secondary lung lobule until there is actually a large air pool with only the connective tissue septae remaining. In this large lung section, the black lines indicate the extent of the bullous fields and give some indi-

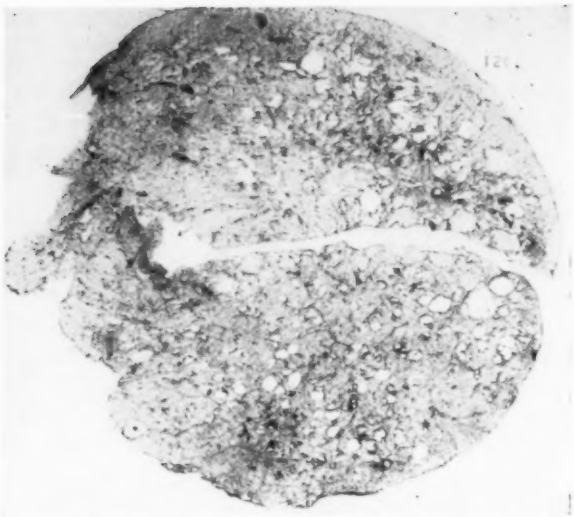

FIG. 64. Severe centrilobular emphysema in a St. Louis civilian.

cation of the tremendous amount of pathologic dead space. I might add that we are now attempting to correlate the anatomic dead space with functional residual volume determinations.

Because of insufficient data I am not in a position at this time to go further into this correlation between functional findings and morphologic extent (figures 65 and 66). The correlation of tissue alterations in terms of clinical disturbances is, of course, going to be an exceedingly difficult one, as one of the earlier speakers this morning indicated. The large lung sections clearly point out the remarkable variation in extent of the disease and seriously challenge the value of "bucket biochemistry" on a large bullous field or an extensive band of scar.

In contrast with the generalized centrilobular emphysema, there is another type, equally distinctive, much more frequently observed, which very often is a background pattern observed in cases of centrilobular emphysema. We have seen about 20 cases of this type, which we currently label pure generalized panlobular emphysema. The bulk of our material in advanced emphysema has been of the diffuse panlobular type on which there is a superimposition of the punched-out central lobular emphysema. The etiologic background to panlobular emphysema must await serial section and histologic study, but its gross pattern would infer that the primary lobular alterations of distention are not closely allied with terminal bronchiolar disease. The panlobular emphysema is diffuse throughout the lung and throughout all lobules (figures 65 and 67). It is for this reason that we have used the word "panlobular" in contrast to the central situation as observed in the other form of common generalized nonindustrial emphysema. Bullous fields are not as commonly encountered in diffuse panlobular emphysema. It would be our opinion that the presence of bullous fields on a background of panlobular emphysema is probably indicative of the superimposition of the centrilobular type.

The question remains, but probably cannot be answered at this time, whether one has the right or the knowledge to separate these two distinctive types of emphysema solely on the macro pattern. But there is a rationale for this. The coal pigment distribution in panlobular emphysema is quite different from that which is observed in centrilobular. In panlobular emphysema the coal pigment is scattered in a diffuse fashion throughout the lobule without concentration or mantling around the central bronchiolar emphysematous area (figure 68). In essence, panlobular emphysema appears to represent permanent overexpansion or pathologic distention of the entire lung. One of our cases of generalized panlobular emphysema has been observed in a woman who

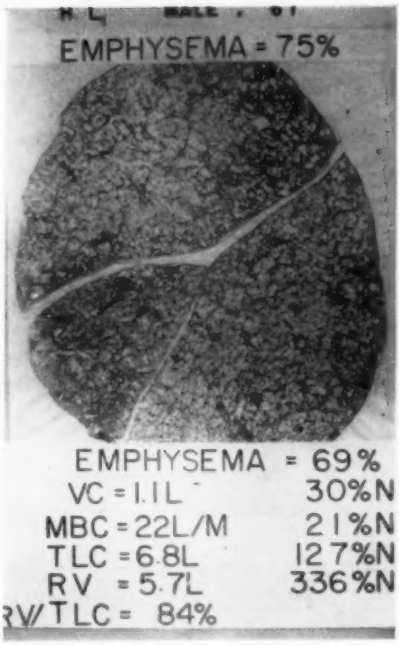

FIG. 65. Correlation between clinical, physiologic, and pathologic findings in a case of emphysema.

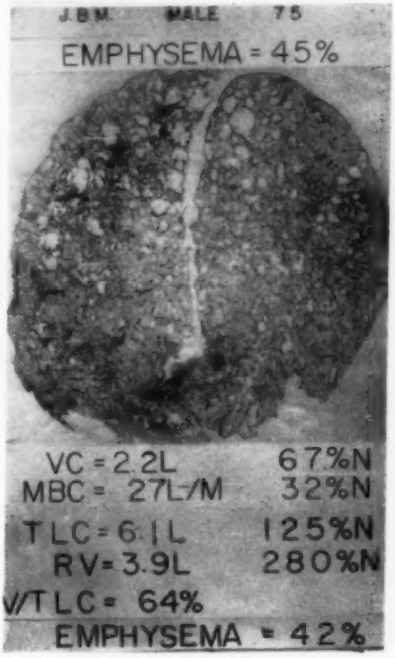

FIG. 66. Same as figure 65.

has had classic asthmatic attacks for some forty years, and she showed the presence of only the panlobular type. Another was observed in a young man who had advanced rheumatoid arthritis of the spine and also pulmonary hypertension. The arthritis of the spine was so advanced that the prosector actually performed the autopsy with the cadaver in the sitting position! In this particular case the panlobular emphysema was concentrated in the central portion of the whole lung with freedom of the outer peripheral portions. What this gross distribution means I do not know yet, but we have observed it several times previously in young men who have neuromuscular paralysis and have permanent sequelae of prominent muscular distortion and bony deformities. The concentration of emphysema appeared to be in the gross central portion of the lung. This is an advanced form of bullous emphysema, generalized panlobular type, in which the margins of the bullous fields are indicated by the large vessels demonstrated by the red latex within them. I prefer to use the term bullous field rather than speak of an individual bulla or blebs.

In addition to the use of the macrosection, the remaining lung was used for permanent plastic casts of the respiratory tree and the vascular pathways. In advanced chronic bronchitis with generalized emphysema, there is a pronounced "withering" of the capillaries with considerable tortuosity and angulation and dilation of the pulmonary artery; and, in addition, numerous vascular abnormalities are noted with regard to the pulmonary venous side; the veins are tortuous and present a verminous outline. Dr. Liebow has previously referred to this vascular disturbance and has demonstrated the alterations in the pulmonary venous channels. In the same lung, a marked alteration may also be seen in the major bronchi proximal to the bullous fields. The emphysematous bullae observed in the large lung section now appear in this fashion with the white latex presenting these unusual, bizarre, plastic configurations. The bizarre appearance of these

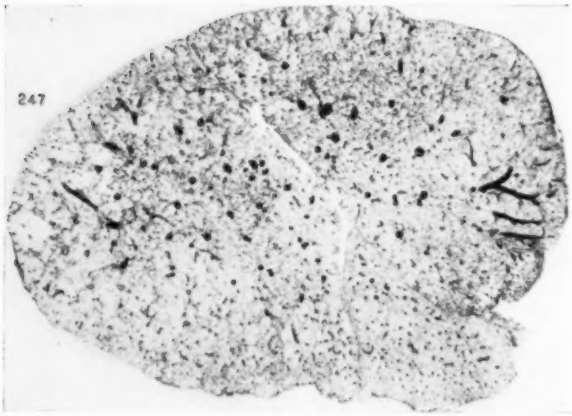

FIG. 67. Pure generalized panlobular emphysema (not centrilobular).

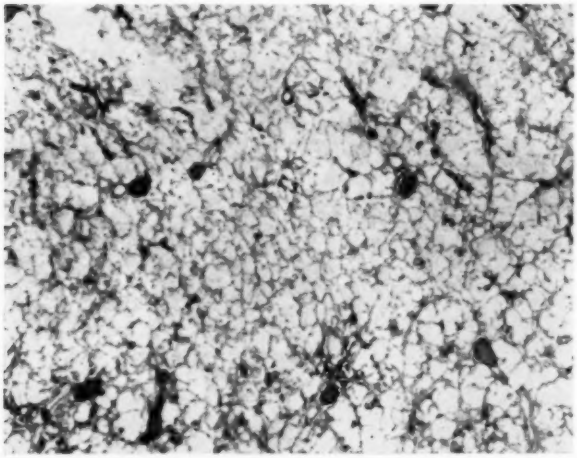

FIG. 68. Same as figure 67, higher power, showing distribution of coal pigment throughout lobule.

bullous configurations was referred to some years ago by Loeschcke. In his preparations he used Wood's metal for corrosion studies of the lung.

With the injection of latex and subsequently the production of a paper-thin section of the whole lung, it is often possible to discover unsuspected vascular shunts within the lung; for instance, around a carcinoma of the lung. With the injection of the red latex into the arterial tree, a cavernous hemangioma may be noted on the periphery of the cancer. We have one other such case as this. Dr. Ebert, I believe, has previously demonstrated the existence of vascular shunts in the periphery of carcinomas of the lung. The same type of shunt can be seen in the apex of the lung, such as the periphery of a segmental emphysema or on the edge of an established case of paracicatricial air cyst formation. The last case is that of a man who was an arc welder; the large lung section revealed occult carcinoma of the lung, the extent of diffuse interstitial fibrosis apparently attributable to cadmium fumes and, finally, the presence of a shunt.

There is no question that the macrosection is the ideal way of demonstrating and producing an extremely informative morphologic map. Most

of these changes in this last case would certainly have been missed if the routine method of taking one or two tortured sections for histologic examination had been performed. As the time has run out on this presentation, and I am running out of breath, perhaps I should conclude because, although pathologists always have the last word, we are surrounded by clinicians and agree with Hamlet that, "In this harsh world we shall take our breath in pain."

MICRORADIOGRAPHIC TECHNIQUES FOR STUDY OF EMPHYSEMA[1, 2]

CHARLES P. ODERR, PHILIP PIZZOLATO, AND JOSEPH ZISKIND

Introduction

The difficulties encountered in studying the macro-anatomy of emphysema are somewhat similar to those that would be encountered in studying the holes of three-dimensional doughnuts with most of the doughnut gone. If the walls of a hollow three-dimensional polygon were intact, one might reasonably expect to reconstruct an image of its size and shape through study of serial sections. In emphysema, however, not only have many of the wall sections partially or totally disappeared, but many of the anchoring corner angles have either been distorted out of recognition or ruptured or retracted. If the difficulties of dealing with tissue almost as fragile as cobwebs are added to this, it is understandable why the anatomy of emphysema has been difficult. Taking advantage of newly developed beryllium-window X-ray tubes and of dry-inflation fixation of lungs, we studied 146 lungs in the following manner:

Methods and Material

For inflation-drying, air flow pressure in the main bronchus of 25 to 30 cm. of water was found to be sufficient for most lungs[3] (1-3). In the latter part of the study, 500 ml. of 95 per cent alcohol were introduced into the main bronchus to aid in fixation. This was done when the lung was first put up for drying. Drying was complete in four or five days. A powered circular-blade meat slicer was used to cut slices from a few tenths of a millimeter in thickness up to 2 cm. Sagittal, frontal, and cross-section planes were used. Cross-sections were preferred because they were easier to handle.

The slices were inspected by various powers of magnification from × 2 with a reading glass to × 90 with a dissecting microscope. Under the binocular microscope, resections of portions of individual dilated air-sac walls were made, using retinal scissors. When the resected air-sac walls were flattened out under a cover-slip or floated on glass slides, they were suitable for microphotography either as stained or unstained specimens.

The following roentgenographic techniques were developed: Large slices a half-millimeter thick were sandwiched between a film and an intensifying screen inside a tight-fitting cassette. Single emulsion film was used or the emulsion on one side of double-coated film was excluded from the developing process. Exposure factors are given in the technique chart (table 1). An entire cross-section slice through the lung could be "photographed" at one time using the fluorescence from an X-ray intensifying screen in this manner. Another method used occasionally for thin translucent specimens was direct photographic enlargement. A shadowgraph enlargement of ten times could easily be obtained in this way. For the thickness range between 0.5 to 2 mm., we used discs of tissue about 3 cm. in diameter. These were roentgenographed in a vacuum chamber using 2.5 kilovolts. The Philips microradiographic unit (1 to 5 kilovolts) was used, but a longer "camera" was constructed so that a larger area of the specimen could be radiographed than is permitted with the standard equipment. Evacuation of air from the chamber of the "camera" was accomplished by a simple faucet suction pump. At a distance of 13 cm., using Eastman Fine Grain Positive film, the average exposure time was three minutes.

For the thickness range above 2 mm., the General Electric grain unit was satisfactory, using from 10 to 30 kilovolts. No vacuum chamber was used with this technique, but the exposure was carried out in the dark in order to avoid the necessity of film holders. The minimal distance available on the grain unit would radiograph an area about 6 cm. in diameter. This was appropriate when using 10 kilovolts through air, but the distance (and therefore the size of the field) could be increased rapidly as thicker slices were used and the higher kilovoltage became appropriate. The entire dried lung was roentgenographed, using the 20 to 30-kilovolt range. For the thicker slices and the whole lung, Eastman Type M. Industrial X-ray film was used instead of Fine Grain Positive.

In order to show that the defects were not produced by overinflation with air, we performed the following experiments:

A freshly autopsied lung was filled with warm liquid gelatin and placed in the cold room overnight. The following morning, when the gelatin was solidified, the lung was sliced, revealing defects similar to those seen with the inflation-drying technique.

A fresh lung was filled with and submerged in 10 per cent formalin, with similar results.

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[1] From the Veterans Administration Hospital, New Orleans, Louisiana.

[2] This study was aided by a grant (No. C-3200(C2)) from the Institute of Pathology of the National Institutes of Health, U. S. Public Health Service; and from the Research and Education Division of the Veterans Administration.

[3] We formerly used 15 to 20 ml. of water pressure, but eventually realized that this was responsible for the circumscribed type of central zone pathology described in a previous paper.

TABLE 1

MICRORADIOGRAPHIC TECHNIQUE

Specimen	Kilovolts	Milliamperes	Time	Distance	Film Holder	Type of Film	Tube	Developer
Whole dry lung G.E.*	20	5	3 minutes	30 inches	None (Specimen directly on film)	Kodak Indus "M"	0.08 Be, 0.7 mm. focal spot	Regular X-ray film developer
2 cm. thick slice G.E.*	10–15	3–5	3–3.5 minutes	10 inches	None (specimen directly on film)	Kodak Indus "M"	0.08 Be, 0.7 mm. focal spot	Regular X-ray film developer
3 mm. thick slice G.E.*	10–15	3–5	3–12 minutes	2.5 to 10 inches	None (specimen directly on film)	Kodak Fine Grain Positive	0.08 Be, 0.7 mm. focal spot	Kodak Dektol
2 mm. thick slice Philips†	2.5	2.5	3 minutes	13 cm.	None	Kodak Fine Grain Positive	50μ Be, 0.3 mm. focal spot	Kodak Dektol
1 mm. thick slice Philips†	1.5	2.5	3 minutes	3 cm.	None	Kodak Fine Grain Positive	50μ Be, 0.3 mm. focal spot	Kodak Dektol
Below 0.5 mm. Fl. photo‡	120	10	2 seconds	40 inches	Casette, Radelin TD screen	Type "M" (single emulsion)	0.3 mm. focal spot	X-ray film developer
Below 0.5 mm. Fl. photo.‡	120	10	12 seconds	40 inches	Casette, Radelin TD screen	Kodak Fine Grain Positive	0.3 mm. focal spot	Kodak Dektol

* General Electric grain unit.

† Philips CMR-5 microradiographic unit. Three-centimeter film holder is supplied with machine; 13 cm. holder constructed. Specimen is directly in contact with film. Vacuum chamber used.

‡ Fluorescent photograph, produced with a regular diagnostic X-ray machine having a 10-milliampere setting and an 0.3 mm. focal spot.

A few lungs were inflated and dried by producing a reduced pressure around the surface of the lung rather than by introducing increased pressure through the bronchus. The defects in the slices and roentgenograms of these lungs were similar to those which were inflation-dried by increased pressure through the bronchus. Overdistension of the normal lung with as much as 140 mm. of mercury (about ten times normal inflation pressure) did not cause lesions to appear.

Although emphysematous foci were revealed in many unsuspected cases, they were absent in some cases prepared by the same technique, and they were correspondingly severe in every case in which the clinical evidence indicated advanced pathology.

One hundred and twenty-five human lungs, including those of 6 infants and one child, were processed. In addition, lungs from 20 dogs and one gorilla (eighteen months old), all autopsy material from a private veterinary practice, were studied. Most of the human material came from the Veterans Administration Hospital morgue in New Orleans, but lungs from 21 patients were from the city morgue and Charity Hospital, including one woman, one child (age fourteen), and 6 infants. One lung from an adult was obtained from Hines Veterans Administration Hospital in Illinois. Emphysema was considered a major clinical diagnosis in only 14 of our cases. Excluded from the study were known tuberculous patients, most of those who were dying of bronchogenic carcinoma, and others with lung or pleural disease

TABLE 2

NUMBER OF PATIENTS IN VARIOUS AGE GROUPS

Age Category	Number of Cases
Stillborn	2
5 to 24 hours	2
1½ to 2½ years	2
14 years	1
20–29 years	5
30–39 years	15
40–49 years	18
50–59 years	12
60–69 years	54
70–79 years	11
80 years and older	3

TABLE 3

ARBITRARY OCCUPATION CATEGORIES

Category	Number of Cases
Farmers	6
Wood products contact	10
Oil products contact	15
Other outdoor jobs	30
Non-dusty indoor jobs	21
Indoor jobs with dust contact	14
Unknown	22
Infant or child	7

TABLE 4

REPORTED SMOKING HABITS

Reported Smoking Habits	Number of Cases
Non-smoker	12
Light (½ pack)	36
Moderate (1 pack)	19
Heavy (2 packs)	1
Unknown	50

so far advanced that neither lung could be maintained sufficiently intact for inflation-drying techniques.

As noted in the tabulation given in table 2, the ages varied from stillborn to eighty years. A great variety of urban occupations were represented, as well as 6 farmers (table 3). Most of the patients had lived in New Orleans or environs for many years. Although industrialization of this city has increased rapidly in the last few years, New Orleans would not have ranked as highly industrialized during the lifetime of these patients.

RESULTS

About 50 per cent of the human lungs examined were considered to have 1-plus or more involvement on a 1 to 7-plus scale. Most of the others showed small lesions on careful scrutiny. The 14-year-old boy had 2-plus central zone involvement, suggesting that the same or similar disease may begin in early life.

No correlation of severity of emphysema with a *reported* degree of smoking was found. Those with non-dusty indoor occupations had less total disease than those judged to have indoor trades associated with some dust contact. Outdoor workers showed slightly less disease than the latter. The statistical data for various categories still require further testing with larger series.

The disease was found in only 2 of 20 dogs. This may prove to be significant from the standpoint of anatomic, physiologic, or immunologic factors in etiology. Dog-lung anatomy was simpler in design than human-lung anatomy. The size and rigidity (as indicated by the amount of cartilage) of corresponding bronchi seemed to be greater. The gorilla, whose lung structure more closely resembled human lung than did dog lung, showed early central zone lesions.

The patterns of anatomic change to be described relate to: (*1*) the distribution of early lesions in various parts of the individual secondary lobules, and (*2*) the appearance of defects (fenestrations) in individual dilated air-sac walls, and associated soot nodules.

The earliest lesions were usually around some part of the periphery of the secondary lobule, especially near a venule or around a branch of the more centrally located arteriole or bronchiole. Perivascular involvement was apt to be on one side of the vessel only, if the vessel was a major arteriole or venule of the secondary lobule; but perivascular involvement of the smaller vessels was apt to completely surround the vessel. The immediate perivascular area sometimes developed into a minute granuloma-like nodule with variable numbers of fibroblasts and soot-ladened phagocytes, and often with calcification. The cross-section of the entire lung always showed various degrees of nonuniformity in the degree of the chronic emphysematous process, usually based on a recognizable secondary-lobule pattern. No case of uniform chronic emphysema throughout one lung, or even one entire lobe, was found.

The distribution of soot deposit in close relationship to early emphysematous lesions within the secondary lobule was well demonstrated in many of the adult human cases. The major quantity of soot was in the perivascular lymphatics. Small particles were scattered

throughout the neighboring alveolar walls. Larger aggregations were collected in the granuloma-like nodules mentioned above.

Widespread interstitial fibrosis was found in about 4 per cent of the human autopsy cases and, in these cases, large bullae had not developed. Islands of normal tissue remained even in extensive areas of fibrotic honeycombing.

The findings at the level of the individual air-sac walls were related to (*1*) air-sac wall fenestrations, (*2*) remaining tendrils, (*3*) soot-stained nodules clinging to remains of alveolar walls or free in alveolar lumen:

(*1*) The destruction and gradual disappearance of air-sac *wall sections* seemed to be accomplished by the development of multiple fenestrations. It was clear that the fenestrations developed early in the disease process, but a precise quantitative relationship between dilatation of the air sac as a whole and fenestration of individual wall sections was not established. From both stained and unstained preparations of air-sac walls, it was evident that the abnormal openings occurred in the thin areas of the walls between the bundles of elastic fibers. The translucency and staining characteristics of a desquamating area often clearly differentiated it from the surrounding tissue. The size of the initial area, usually ovoid in shape, varied considerably. All stages in degree of completeness of the débridement were seen. A clear sharp rim was seen around the entire circumference of the older fenestration. A similar fenestrating process was seen in some of the secondary lobule septa.

(*2*) The "corners" of adjacent destroyed polygonal wall sections remained as *tendrils*. The tendrils had undergone variable degrees of elongation and attenuation or had ruptured.

(*3*) The soot-stained nodules found free or clinging to the remains of alveolar walls were composed of soot-containing phagocytes and degenerating epithelial cells.

Examples of the various conditions may be seen in the figures at the end of the article.

Comment

Other investigators (4–6) have found evidence of unexpectedly high frequency of chronic pulmonary emphysema when the lungs were carefully studied by some type of inflation technique. The Gough-Wentworth (7) formalin technique has been most frequently used, but the macroscopic detail available is not as good as it is by inflation-drying. The findings in regard to frequency have implications for any situation in which explosive decompression is a hazard because the air in the bullae probably tends to be trapped.

At the secondary-lobule level the beginning of disease tends to be: perivascular and peribronchiolar or subadjacent to pleural and septal surfaces. The common anatomic "denominator" for these two loci may be their proximity to channels of lymph and tissue fluid flow. The selective deposition of the retained soot particles in the region of the earliest emphysematous lesions and in the advancing front of the extending lesions suggests that the deposition preceded rather than followed the development of the lesions. Since the *amount* of soot and amount of disease are not always correlated, it is suggested that the quantitative relationship might be with the amount or kind of leached-out soot products or with the amount of blockage to normal tissue fluid flow.

The emphysema which is formed in the immediate vicinity of granuloma-like lesions or soot nodules (2) is similar to that described by Gough (4) and Heppleston (5, 8) in coal miners. A similar type of emphysematous disease is seen about miliary tubercles and in other diseases which develop small fibrotic foci.

The "enlarging window" formation in the septa is believed to be the most important basic mechanism in the development of chronic emphysema. Besides representing lost capillary surface, each fenestration is a means of abnormal air transfer between two abutting alveoli. This interferes with the smooth and accurate adjustment of bronchiole intraluminal tension at the beginning of expiration. In consequence of this, a check-valve mechanism develops in some of the bronchioles in the following way. Tension which the air sacs are unable to develop *intralumenally* in the bronchiole is transferred *extralumenally*. In other words, the lung (air-sac) tension tends to *compress* the bronchiole lumen rather than to *aid* in its patency during expiration. The lungs apparently still retain a large amount of elastic tissue, but they lose the ability to use it effectively, because the dehiscent-ridden air sac will no longer force the air back out through the bronchiole.

Summary

Slices from 146 human and animal lungs have been studied by various translumination and microradiographic techniques. The loci of origin of emphysema within the secondary lobule have

been described. Both the loci of origin and the character of the relationship of soot deposits to early lesions in adults suggest that noxious substances leached from the soot, or impaired tissue fluid flow resulting from soot aggregations, may be of etiologic significance.

The abnormal fenestrations which develop in the septa between air sacs and the manner in which these could be responsible for functional bronchiolar obstruction have been described. Since the anatomy of emphysema resembles a cluster of empty spaces surrounded by holes, it is not surprising that traditional pathologic methods have been inadequate.

The technical help of Michel Dauzat, Edward Montamat, Orris H. Fontaine, William Bohon, and Joseph Hunter is gratefully acknowledged.

Appreciation for services and advice are due to Dr. Charles Dunlap, Emanuel H. Bresler, Robert Simmons, Hurst B. Hatch, Nicholas J. Chetta, Rudolph J. Muelling, William T. Eckert, Lionel Cazenavette, and J. P. Thrasher.

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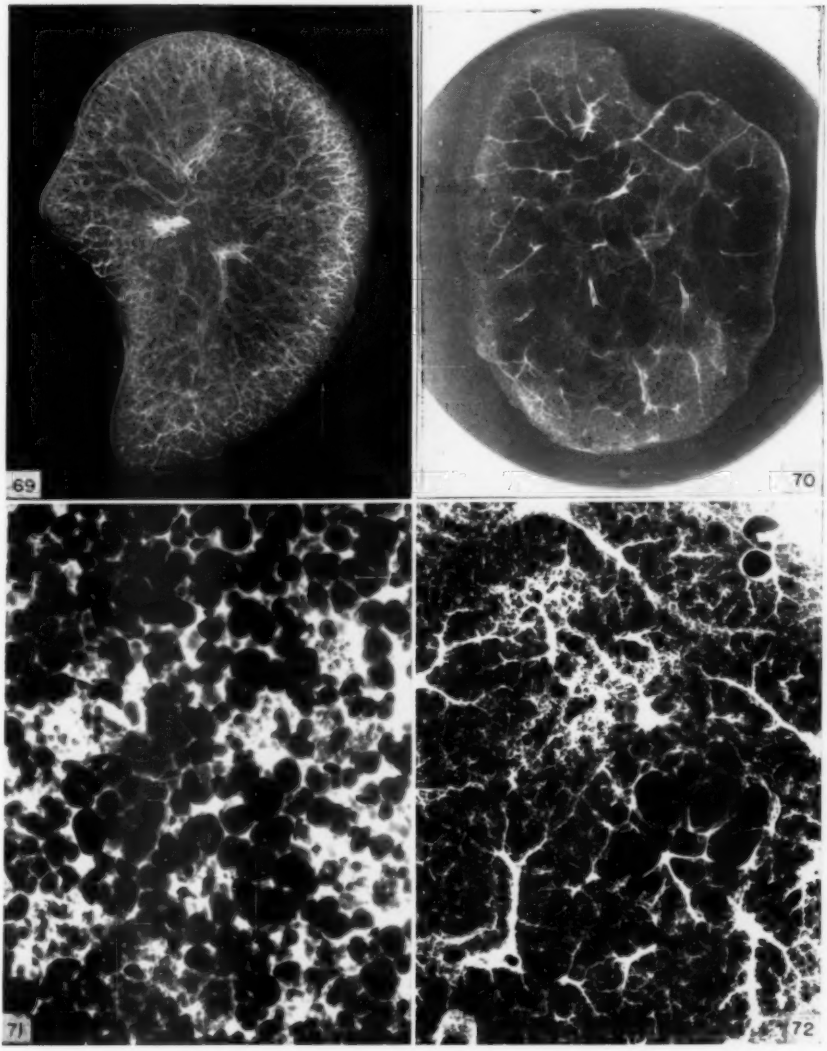


FIG. 69. *Case 38.* Cross-section of normal lung from a 65-year-old Negro male. Note numerical density of arterioles and venules in cortical zones as compared with central zone. Slice is 4 mm. thick.

FIG. 70. *Case C-14.* Advanced emphysema in case having 1,000 cc. more residual air than normal. This approaches generalized emphysema more than most cases. Nevertheless, vast differences exist between different blocks of tissue. 4 mm.-thick slice.

FIG. 71. *Case 68.* Example of advanced interstitial fibrosis showing islands of normal tissue among the honeycomb formation. Enlargement × 10 of an 0.5 mm.-thick slice.

FIG. 72. *Case 105.* Slightly to left and above the center of the picture is an early emphysematous lesion with surrounding density due to soot. The more advanced lesion (below and to the right) shows less soot density, there being nothing left to which the soot can cling.

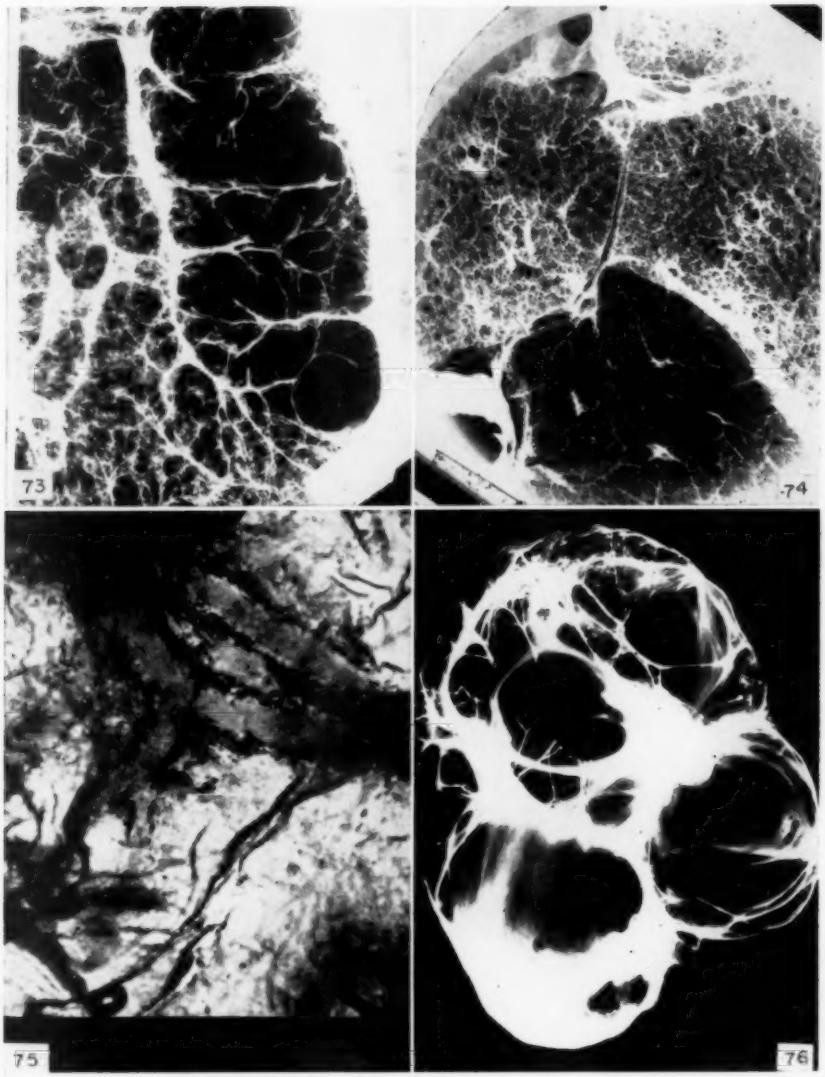


FIG. 73. *Case 93*. Showing emphysema development in the region of a particular set of interdigitations between branches of an arteriole and venule.

FIG. 74. *Case 103*. Lobule in lower center is ischemic. Note that it has *not* developed the soot deposits and accompanying emphysema which are seen in the upper lobules.

FIG. 75. *Case 43*. Dense soot deposit in perivascular lymphatics or lymphatic spaces.

FIG. 76. *Case 86*. Bulla at apex showing tendril remnants of alveoli, some of which show soot nodules clinging to them.

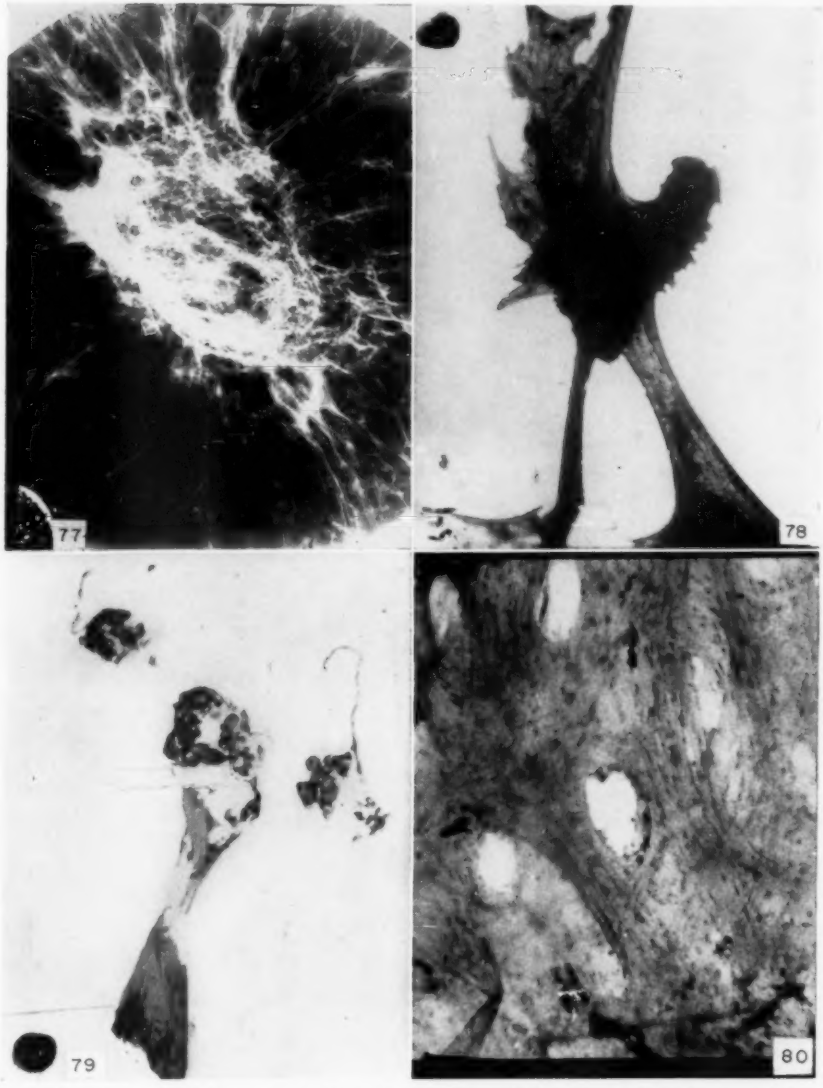
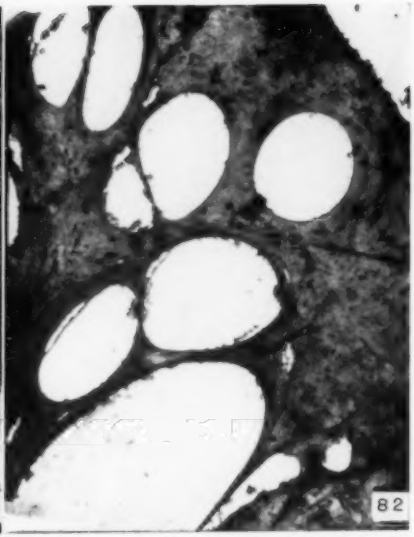


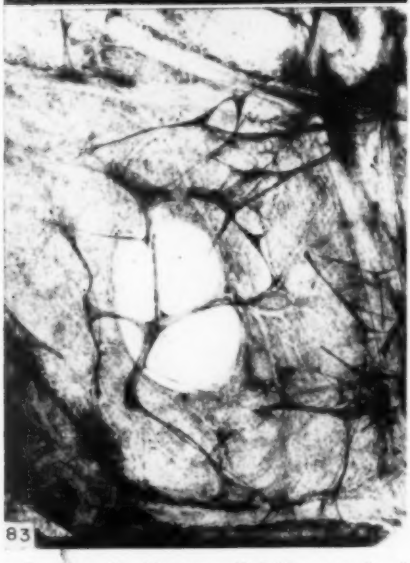
FIG. 77. *Case C-15.* Projection microradiograph of a soot and fibrous nodule with surrounding emphysema. (*Courtesy, Research Department, General Electric X-ray Corporation*)

FIG. 78. *Case 62.* Soot nodule clinging to remaining tendril in an area of advanced emphysema.

FIG. 79. *Case 62.* Section through a remnant tendril with nodule. Brittle nodule splits up when cut. Contains carbon and some calcium.

FIG. 80. *Case 103.* Wall of a dilated air sac showing dehiscences developing between the elastic bundles.





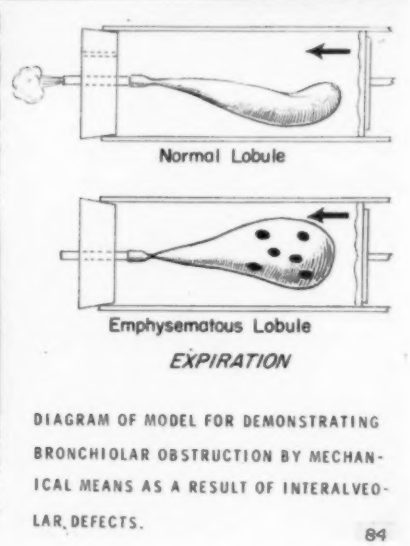

Normal Lobule
Emphysematous Lobule
EXPIRATION
DIAGRAM OF MODEL FOR DEMONSTRATING BRONCHIOLAR OBSTRUCTION BY MECHANICAL MEANS AS A RESULT OF INTERALVEOLAR DEFECTS.
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FIG. 81. *Case 42*. Air-sac wall dehiscence showing differential staining in the desquamating cells around margin of the fenestration.

FIG. 82. *Case 102*. Wall of dilated air sac with numerous fenestrations.

FIG. 83. *Case 108*. Fenestration in wall of interlobular septum. Remnant tendrils of destroyed alveoli on this side of septum visible.

FIG. 84. The model of the *normal* lobule during expiration shows how the *balloon* deflates when the pressure of its surroundings changes from negative to positive. The *neck* of the balloon does not collapse in spite of the increased pressure surrounding it because the "inspired" air is available and under sufficient tension to overcome the external pressure and keep the neck of the balloon open.

The model of the *emphysematous* lobule has holes in it permitting free access of the "inspired" air to the surrounding spaces, which represent adjacent air sacs, some of which surround the neck of the balloon. The *neck* of the balloon does collapse when the pressure surrounding it increases because part of the "inspired" air which should have remained on the inside of the sac to help keep its neck open is now on the outside and helping to compress the neck rather than keep it open. The *balloon* itself does not collapse. The principle by which excessive residual air is maintained is thus illustrated.

General Discussion

Dr. Charles Gaylord (Denver, Colorado): Dr. Oderr is to be congratulated on the use of roentgenographic methods in the exploration of the anatomy and pathology of the lung. This method is relatively undeveloped and deserves further investigation. The material presented reflects, to some extent, the problem: "what is emphysema"? This afternoon the pathologists have also shown us cases of centrilobular disease, and we are not at all convinced that these patients have the kind of emphysema which concerns the clinician. The concept of the pathogenesis of emphysema as being due to the development of multiple fenestrations between elastic fibers is interesting; if confirmed, using various methods of fixation, it will aid in developing a descriptive picture of the disease. Should the etiologic agent of diffuse obstructive emphysema prove to be primarily related to soot or other common dusts, this would be most surprising.

PHYSIOLOGY

DR. CHARLES S. HOUSTON, *Moderator*

Two committees were appointed: one to advise this conference on the most productive methods of preparing lung tissue for gross and microscopic examination in order to determine the presence, extent, and nature of what we call emphysema; and the other to provide this conference with a definition of emphysema, preferably to include anatomic, physiologic, pathologic, roentgenographic, and clinical considerations. Their final reports, not available until some months following the conference, appear here.

REPORT OF COMMITTEE ON DEFINITION OF EMPHYSEMA

Diffuse obstructive emphysema may be defined as a pathologic state of the lungs presenting the following characteristics: widespread coarse air spaces of markedly variable size and questionable identity; distorted surface contours resulting from the presence of subpleural clusters of such spaces (bullae); tendency of the lungs to remain inflated after the chest is open; excessive volume. Microscopically, the enlarged spaces are seen to be the result of attenuation and loss of pulmonary septal tissues. These pathologic changes are frequently accompanied by clinical symptoms and irreversible alterations in pulmonary function. The chief symptom is dyspnea. Tests of pulmonary performance demonstrate that retardation of expiratory air flow, increase in residual volume, inhomogeneity of ventilation and perfusion, and decrease in diffusion capacity occur in diffuse obstructive emphysema. Late in the disease, hypoxia and hypercapnia occur, and the symptoms and signs of right heart failure may be observed.

DAVID BATES
ALFRED P. FISHMAN
WARD S. FOWLER
PHILLIP C. PRATT
RICHARD V. EBERT, *Chairman*

REPORT OF COMMITTEE ON PREPARATION OF HUMAN LUNGS FOR MACROSCOPIC AND MICROSCOPIC STUDY

The Committee was charged with "advising this Conference as soon as possible on the most productive methods of preparing lung tissue for gross and microscopic examination in order to determine the presence, extent, and nature of what we call 'emphysema'."

A preliminary statement was circulated to all of those attending the Conference for careful study with the request that "at your earliest possible convenience mail your recommendations for changes and/or comments directly to the Chairman." Pertinent suggestions made by several members attending the Conference have been incorporated into the final draft. Among these have been the inclusion of selected references of published investigations on pulmonary emphysema in which methods of lung preparation similar to those recommended by the Committee have been employed. After further consideration by the Committee it seemed important to recommend that the lungs of man, regardless of the nature of the disease, be routinely prepared for study by the methods described below.

It is the considered opinion of the Committee that much of the diversity of views concerning the pulmonary changes associated with emphysema and other diseases is due to the variety of methods and staining procedures which are employed by different investigators in studying the lungs. The lungs, because of their elastic tissue content and vesicular construction, undergo varying degrees of collapse and distortion following death. Additional bizarre changes result when they are handled and examined in the fresh state, then fixed by simple immersion.

In order to obtain a more uniform interpretation of the lung changes associated with symptoms of

pulmonary diseases including emphysema, it is recommended that the lungs first be fixed *in toto* via the air passages before they are sectioned for macro- and microscopic examination.[1]

This can be done easily with the lungs *in situ* or following their removal from the body along with the trachea. In either case a ligature should be placed about the base of the heart or around the pulmonary artery and veins to prevent exsanguination of the lungs and vascular collapse when the lungs are re-expanded by the fixative.[2]

An all-purpose fixing solution containing 10 per cent neutral formalin and 5 per cent sodium acetate is recommended.

Autopsies on suspected cases should be performed as soon as possible after death. To fix the lungs *in situ*, the sternal plate is removed and the pulmonary vessels tied. The trachea is dissected free. A cannula attached to a rubber tube and funnel is inserted into the trachea and tied. The fixative then is allowed to fill the air spaces under low-gravity pressure (8 to 12 inches) until the lung borders show their normal contours. The trachea is then tied to hold the fixative in the lungs. Replacing residual air with carbon dioxide, which is soluble in fixing solution, aids in fixation (Tompsett).

When the lungs are removed before fixation, they should be suspended by the trachea in a large cheesecloth bag or floated in a pan of fixative. With low-gravity pressure (8 to 12 inches), they are then re-expanded with fixative until the normal contours of the inflated lobes are re-established.[3]

The filled lungs should be submerged in the same fixative for at least three days (up to ten days is preferable to insure inactivation of enzyme activity) in a container sufficiently large to avoid compression and distortion of tissues.

For macroscopic study, Gough's, Cunningham's or Wyatt's methods of sectioning are suitable (large section microtome, long knife, or mechanical meat cutter). Multiple sections from normal and abnormal parts of the lungs should be taken for microscopic examination. These should be imbedded in paraffin or celloidon under vacuum. Most pathology laboratories employ these procedures routinely.

Both thin (10μ) and thick (50 to 100μ) aerial sections and staining of alternate slides by: (*a*) hematoxylin and eosin or hematoxylin-eosin-azure II for cellular detail; (*b*) orcein or Weigert's procedures for elastic fibers; and (*c*) Mallory's azan (azocarmine methylene blue orange) stain for collagenous fibers and pulmonary capillaries are advised. Silver stains for reticular fibers can

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[1] *Comment by Dr. A. A. Liebow:*

In my opinion, the method recommended for fixing lungs is fine for many purposes, and I have been practicing it routinely for surgical specimens and for special autopsy specimens for many years. Of course, the vessels come tied in lobectomies and pneumonectomies.

For emphysema, however, the additional procedure of fixing lungs in a state of collapse should be employed. If this is not done, the lungs are displayed only in a position comparable to inspiration. "Valves" similar to those illustrated in the recent paper by Leopold and Gough (Thorax, 1957, *12*, 219, figures 7 and 8) will be shown only in the "open" state. My suggestion, therefore, if the disease involves both lungs as it usually does, is to fix one lung as recommended by the Committee, and to fix the other in a state of collapse by simply cutting sections of the whole lung with a long sharp knife from the pleura to the hilum, at a thickness of approximately one inch. These are then fixed in a large flat pan of fixative. Submersion is aided by placing cotton wet with fixative on top of the upper surface. A vacuum chamber is, of course, desirable, but not generally available in this size. When the specimen has been fixed for three to four days, thinner blocks suitable for embedding are cut and refixed. Artifacts will exist in these lungs, but they are useful for comparison with others fixed by the intrabronchial insufflation method.

[2] *Comment by Dr. C. J. Martin:*

I have been wondering why a ligature should be placed around the base of the heart and around the pulmonary artery to prevent exsanguination of the lungs and vascular collapse when it would seem that the vascular structures might well be filled with the same fixative if they were cannulated and the same low-gravity pressure was allowed to fill the vascular structures even as the lung was being filled. I also wondered whether some statement as to electron microscopic preparation should be made.

Committee answer (Dr. Loosli): (*1*) Tying the blood vessels is more simple than fixing by both tracheal and vessel routes; (*2*) preparation of lung tissues for electron microscopic study requires entirely different fixatives and different methods of handling.

[3] *Comment by Dr. R. E. Hyatt:*

I do feel that the pressures which are used to inflate the lung should be standardized. I would suggest that 15 to 20 ml. of water be used. With excised lungs, I would place the lungs in a large container of fixative and then adjust the height of the reservoir delivering fixative intrabronchially so that a pressure head of 15 to 20 ml. of water exists between the top of the reservoir's fluid level and the fluid level in the large container. The lungs may tend to float and kink so that intrabronchial fixation will be difficult. . . . In lungs being fixed *in situ*, I guess the middle of the lung should be taken as the reference pressure level.

also be applied following this method of fixation. Details of the above procedures can be found in the appended bibliography.

If only small sections of fresh lungs are to be studied, they should not be more than 0.5 cm. in thickness and should be fixed in a vacuum jar to aid penetration of the fixative. It must be recognized, however, that collapse and compression of tissue by even the sharpest instruments will add their distorting influences to those of the fixatives. Simple collapse alone may account for a reduction of alveolar diameters of approximately 40 per cent. Formalin fixation in the collapsed state reduces these by another 12 per cent.[4, 5]

When experimental studies on emphysema are done, the lungs of the animals should be fixed and stained as recommended above; otherwise *en face* views of interalveolar septa will seldom be seen, and alveolar pores, elastic and collagenous fibers, capillary networks, and other structures important to the recognition of the presence and extent of the disease will be altered in form and size.

When a thorough macroscopic and microscopic study of the lungs has been made, the clinician, radiologist, and pathologist should correlate their findings with those recorded in the clinical history.

In this way differences can be resolved and more meaningful data assembled which will shed light on the pathogenesis of pulmonary emphysema and other lung diseases in man.

VERNON E. KRAHL
CHARLES E. TOBIN
JOHN P. WYATT
CLAYTON G. LOOSLI, *Chairman*

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[4] *Comment by Dr. H. G. Dayman:*

I like the notes on the preparation of the specimen. Two thoughts come to mind. There is more emphysema (incidence) than is dreamed of in our philosophy, and it would not seem amiss to recommend in passing that it would do no harm to prepare *all* lung specimens in this fashion. After all, this is usually done with the brain, so precedent is set. Moreover, there are pathologists who do not see the lung—even normal lung—in the structure maintained during life through their entire careers, simply because they do not distend it. The lesions of disease as well as the normal lung suffer from preparation in a collapsed state.

Would not a head of pressure implied by "3 feet" ensure rupture of the pleura? A pressure of 91 cm. is quite a lot. Half the distance between bench and floor is the height I have used and the lungs fill well enough—even using raspberry jello.

Committee comment (Dr. Loosli): This was obviously too great pressure, as suggested in our preliminary report.

[5] *Comment by Drs. E. A. Gaensler and Inga Lindgren:*

The other suggestions concern recommendations for the treatment of *lung biopsies*. Obviously, most post-mortem studies of "suspected cases" will involve either far advanced emphysema complicated by terminal infection and/or heart failure. Lung biopsy is a diagnostic procedure, increasingly employed throughout the country, which may give an opportunity to study early and uncomplicated disease. Our own experiences in this regard suggest that a representative sample of lung can be obtained only if certain surgical technical precautions are observed. These include:

1. Double clamping of the lung wedge with Carmalt or similar clamps with the lung fully inflated; division from the lung between clamps, and submersion in fixative of the inflated specimen with the two distal clamps remaining on the lung wedge.
2. Avoiding "nodules" which may be found occasionally in diffuse pulmonary disease. These are frequently removed by the surgeon in the hope of obtaining a specific pathologic diagnosis. Such nodules are never representative of the "average lung." Frequently it is merely a local area of fibrosis, a small residual tuberculous focus, histoplasmosis, or a silicotic nodule. These are in no way helpful in comparison of lung structure with clinical or physiologic findings.
3. Avoidance of the most dependent portions of the lungs such as the tip of the lingular segment. Such specimens are surgically attractive because they are most easily removed by application of a single clamp. However, such dependent areas are prone to show nontypical changes such as stasis, atelectasis, or edema, all not characteristic of the lung as a whole.

Committee comment (Dr. Loosli): Vacuum embedding is routine in most up-to-date pathology laboratories; biologic houses have ovens.

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MECHANICS OF VENTILATION IN EMPHYSEMA[1]

WARD S. FOWLER

As all of you know, the people who are the mechanics experts are now sitting around the table or in the audience, and I am somewhat hesitant about making this presentation. I hope there will be free discussion of what I consider to be several difficult questions. These questions have, I think, a bearing on the physiology of ventilatory mechanics in emphysema. They are as follows:

1. What is respiratory work?
2. How is the work accomplished?
3. What are the ventilatory results of the work?
4. How is the work perceived?

Consider respiratory work. You have seen illustrations of one of the methods by which the work of breathing has been analyzed, viz., pressure-volume diagrams that have the dimensions of physical work. There are questions in my mind as to how informative this approach will continue to be. One question is: what change of pressure and what change of volume should be measured? The use of esophageal pressure changes leaves something to be desired. The apparent variation of pulmonary compliance when pressure changes have been measured at different locations in the esophagus is disturbing. Another question is whether there is a single value of intrapleural pressure (pressure outside the lung) when the lungs are in natural motion.

Recent measurements in animals by Coleridge and Linden, and older ones by Wiggers, of pressures in various intrathoracic but extravascular locations are not easily reconciled with the concept of a uniform change of extrapulmonary pressure, but indicate the existence of variations in both amplitude and phase. This raises the further question of what volume change should be related to what pressure change. At the mouth one measures the summation of all of the constituent volume changes. One would think the proper pressure-volume work would be the summation of the separate values of pressure-volume work of the individual regions of the lungs. How to accomplish this, I don't know. Moreover, emphysema seems the ideal situation for all sorts of regional mechanical variations.

There is a distinction between physical and physiologic work when the former is measured in gram centimeters. As our subjective impression of muscular work correlates with the product of tension and time, as in supporting a stationary weight, so does the liberation by muscle of "maintenance heat." Moreover, Fales and others have found that some oxygen uptake of skeletal muscle is related more to the number of motor nerve impulses received than to the external work done.

It seems to me that the respiratory muscles have been neglected. Let us grant that mechanical work is done on the lungs by the muscles and that the muscles are activated by motor nerve impulses. We commonly say that the diaphragm in emphysema is depressed, flat, and moves little. Is the top of the liver also flat? But why does the diaphragm not move? Is it atrophied? Is the respiratory center not sending out motor impulses to it? Why does the center apparently choose to send impulses more selectively to accessory muscles, and not send impulses to abdominal muscles to contract and thereby elevate the diaphragm? Perhaps an abnormal afferent input to the center is responsible for the pattern of output.

What are the ventilatory results of the work? In figure 85 the typical nitrogen clearance curves are shown. Analysis of such curves shows that the variation in turnover rates of various parts of the total alveolar gas, normally rather small, becomes very large in emphysema, with large volumes of gas that are very slowly ventilated. This is a quantitative and not necessarily a qualitative difference. The turnover rate reflects the ratio of alveolar ventilation rate to alveolar volume. You will remember Dr. Loosli's presentation of the growth and age changes of the sizes of the air spaces in the lung. If the abnormal size of the air spaces in emphysema is important, what general things do we know about the size of air spaces? First, in mammals, alveolar surface per unit volume seems directly—and alveolar volume inversely—related to metabolic rate. A sloth has very large air sacs, and a healthy old

[1] From the Mayo Foundation, University of Minnesota Graduate School; and the Mayo Clinic, Rochester, Minnesota.

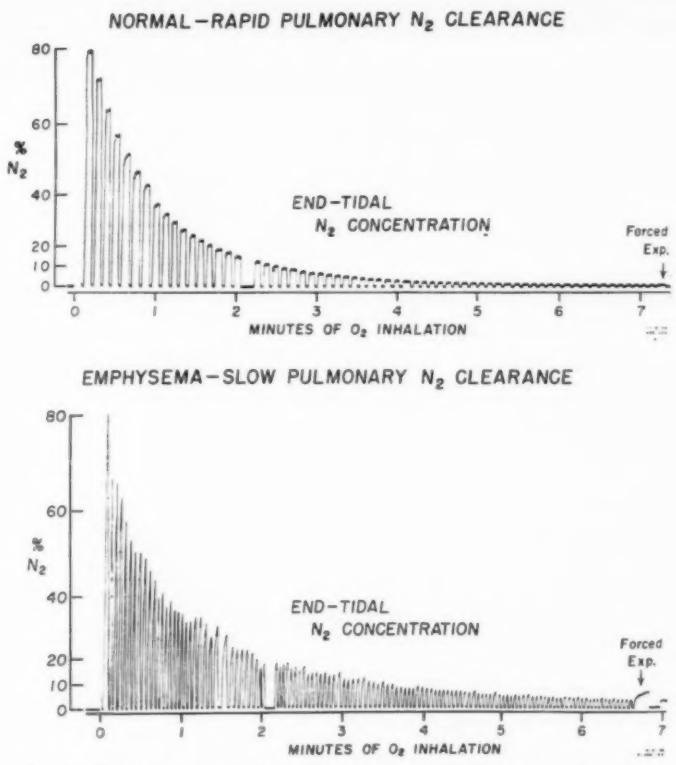

FIG. 35. Typical nitrogen clearance curves: normal and in emphysema.

man with a lower metabolic rate than a young man can get along with larger spaces. In the controversy about the changes of size of pulmonary structures in emphysema (for example, the bronchiolar lumen, which is conventionally described as "constricted" or "dilated"), the use of methods based on spatial measurement should help. It seems that Dr. O. R. Hunt will be able to apply the Chalkley method to obtain three-dimensional quantitative histologic anatomy of the lungs. Perhaps some day there will be measurement of the total area of the lumina at various places in the peripheral bronchial tree.

To return to the abnormally large variation of alveolar turnover rates seen in emphysema, it was interesting to hear Dr. Oderr's presentation of central lobular emphysema in a 14-year-old boy, if I remember correctly. Nonuniform alveolar ventilation of some degree, while sitting, is apparently usual in healthy adult men. The anatomic location of the differently ventilated spaces is unknown. However, this has not been studied extensively in women and preadolescents, although I believe Dr. Huff in Seattle has data that at least raise the question whether the development of significantly uneven ventilation may be a feature of male adolescence.

Both this line of thinking and the considerations of alveolar size and metabolic rate point to the endocrine system. In considering the metabolic processes and anatomy of tissues, Dr. LeBlond of Montreal once pointed out that the amount of tissue present, readily evident in the skin, depends on the rate of addition of cells and the rate of their loss. As far as I know, the half-life of various human pulmonary cells is unknown, as well as how this is normally regulated. In any case, development of rarefaction or dissolution of peripheral pulmonary tissues would require only that, over long periods, the regenera-

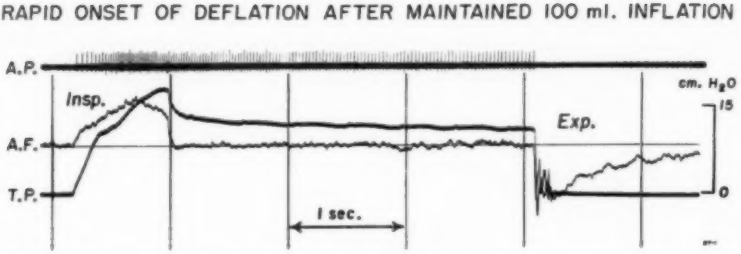

FIG. 86. Recording from anesthetized cat. *AP*—vagal afferent action potentials; *AF*—rate of tracheal air flow; *TP*—transpulmonary pressure. (From Davis, Fowler, and Lambert: Am. J. Physiol., 1956, *187*, 558.)

tion rate be very slightly less than the death rate, regardless of which was altered primarily.

The last question concerns the perception of respiratory effort and dyspnea. I assume that in emphysema at least some of the sensation of dyspnea arises from the pattern of afferent impulses originating in part in the lungs and structures of the thoracic wall. In emphysema are there anatomic abnormalities in the various sensory receptors in the lungs and thoracic muscles, including the diaphragm? This presupposes the existence of similar knowledge about the normal human neuromuscular anatomy. Too little is yet known about the normal neuromuscular physiology of the breathing apparatus, in which the function of the chest wall and lungs must be regarded not in isolation, but as part of the same system.

One aspect in which we have been interested is the vagal afferent impulses from stretch receptors in the lungs. Unfortunately, the impulses from such single receptors have been studied only in animal preparations. A record, obtained with Drs. Davis and Lambert, of the vagal afferent impulses, or action potentials, from a slowly adapting stretch receptor of a cat's lung is shown in figure 86. These impulses represent the afferent basis of the Hering-Breuer reflex, alterations of which at times have been very loosely invoked in various diseases. The figure illustrates what is very probably the first "timed vital capacity" ever performed by a cat. Actually, after a large and maintained inflation, the lungs were permitted to deflate very rapidly. Here we can note only several characteristics of the frequency of discharge. It is roughly proportional to the inspiratory work done on the lung, and remains elevated while inflation is maintained by the equivalent of physiologic work. With onset of deflation (and at other times), changes of mechanical conditions are signalled to the central nervous system within a few milliseconds. When one considers the myriad of such detailed information from varied types of sensory receptors constantly going to the brain (the vagus has a direct afferent representation in the cortex, strangely enough, just above the orbits), one is not optimistic about soon being able to achieve more than a very superficial understanding of even the peripheral physiologic basis of dyspnea.

GENERAL DISCUSSION

DR. RADFORD: I would like to comment on some of the points raised by Dr. Fowler, the first question being "Is there an intrapleural pressure?" I don't think he meant this in the sense of "Is there a pressure in the intrapleural space?" The question was "Do we know what it is in any individual at any given time?" His comment on the esophageal balloon is somewhat dismaying to the respiratory "mechanics" in the room here, the reason being, of course, that, if it is not acceptable, it would put a lot of people out of work. Seriously though, we do have to get some measure of what is going on mechanically in the lung, and the esophagus has been used because it is less dangerous than sticking a needle into people. This is particularly true in emphysema. We always have some reservations about the esophageal pressure, but we must work with what we can measure, just as pathologists must work with material as they get it. I hope the anatomists and pathologists here will remember that we do not accept this necessarily as a complete answer to the problem of intrapleural pressure; it is nevertheless what we must work with.

In emphysema I am sure that Dr. Fowler's question is quite valid, namely, "Is there a single

pressure over the outer surface of the lung which can be considered to be active mechanically?" A very simple way that I have of convincing myself that there is such a thing as a single intrapleural pressure in a *normal* lung is to consider what would happen if you took the lung out and inflated it without the chest wall around it. If there were significant differences in the stress in the two situations, one would then intuitively think that perhaps the intrapleural pressure might not be truly representative in a single point. The fact is that in normal lungs the shape of the thorax is very closely simulated in the excised lung. I would ask the people here who have studied the emphysematous lung whether this is true. Judging from the pictures yesterday, I would say that it is probably not true, and thus Dr. Fowler's criticism is valid.

DR. FOWLER: I think the inflated excised lung does fit the shape of the thorax in many circumstances, but does it exactly fit the shape of the thorax when the subject is lying on one side?

DR. RADFORD: I think it is still valid to think of a single intrapleural pressure even in a person sleeping on his side. The question of the external work done by the respiratory muscles is a very pertinent one. I do not think anyone seriously worries about this because we have this mystic idea of the efficiency of the respiratory muscles which we can always talk about. Therefore, I do not seriously worry about the strict relationship between the external work done by the respiratory muscles, the actual oxygen consumed by them, and the actual output of the respiratory center. The respiratory muscles in emphysema (and Dr. Fowler has emphasized this) play a very significant role in the disease process. Perhaps others will comment on this.

I would like to close on the idea raised by Dr. Fowler on the size of the alveolar units as related to the metabolism of the animal. The question is "Which is cause and which effect?"—this faces us all the time. It is interesting to note that the cat, a small animal, has larger terminal alveoli than the dog, which is a larger animal; yet perhaps Dr. Fowler's analysis still holds in that the cat is more languid and perhaps its metabolic rate is different from the dog's, at least in the exercising state.

DR. HENRY WILLIAMS (Valhalla, New York): I would like to ask Dr. Fowler about the nitrogen-dilution curve in emphysema. I think he implied that this is a way to detect early emphysema, and I would like to know by what criterion we should look for early emphysema in the population—a seven-minute nitrogen figure or some ratio of fast-to-slow components? Have we standards of ages and sex which enable us to distinguish people with early emphysema so that we can really distinguish them from the normal by this method?

DR. FOWLER: In a population survey I would not rely only on a nitrogen meter. I would throw that in for information and see what kind of data I was getting out of it. I think it would be mainly a device to help interpret what I was doing because, you see, there is nothing inherently anatomic in this particular measurement. It only represents turnover rates of alveolar spaces. There is nothing inherent in this that tells us that the pattern accompanies emphysema, but it accompanies many other diseases. This has theoretic implications. On a practical basis I would just do some sort of a fast expiration test and separate the people who can exhale rapidly from those who can't. However, I do not intend to imply that this is solely a disease of expiration, for I have no information whether this is true or not.

DR. HANS H. HECHT (Salt Lake City, Utah): The standard gambit thrown in here is the question "Why not use the stethoscope?" Let me parry this insidious thrust which really is said to undermine what we are doing. If the stethoscope had given us all the answers to the problems with which we are confronted and which baffle us, we would not use the other methods.

DR. DAYMAN: I just want to point out that the basis for using the stethoscope was clinical observation originally. There were a lot of mistakes made and the method was condemned, especially by the roentgenologists prior to the physiologists. The physiologists don't treat patients and, even if they diagnose a disease correctly, they leave the patient as he is. But if the stethoscope is used from the standpoint of physiology (working from the physiologic test to the stethoscope), mild bronchitis, for example, can be picked up as quickly as from the study of airflows because it is possible to hear wheezing and note areas of inadequate ventilation. Why should one need to take resort, in routine examinations, to nitrogen dilution curves when large areas can be mapped out by the stethoscope?

DR. HECHT: One hates to argue with an anatomist, but the situation is very much the same in heart disease. We can make a diagnosis of mitral stenosis or mitral insufficiency by the stethoscope very well, but it is the quantitative aspect that we are concerned with. It seems to me that this is where the methods of auscultation and physical examination are not very efficient. In order to meet the quantitative aspect, it is necessary to go to the next 10 per cent in the final total evaluation of the patient.

DR. FOWLER: Dr. Dayman, I don't believe I suggested that it was necessary to use nitrogen meters. May I also add that I think the question of

the various methods of diagnosis will be settled, not by our opinions, but by a controlled experiment. I quite agree with you that the stethoscope is a very useful instrument. It is also my impression from seeing young physicians that somehow our departments of chest medicine have been unable to teach many young physicians the most effective way to use the stethoscope. This, I think, is the responsibility of the physician, not of the physiologist.

Dr. E. Osborne Coates (Detroit, Michigan): Dr. Fowler made a suggestion that in emphysema the diaphragm might have a faulty innervation, and I wonder if there is any evidence for this. Clinically, the impression would be the reverse for, in giving pneumoperitoneum to people with emphysema, it is very difficult to raise the diaphragm by air from underneath.

Dr. Pratt: I think we can touch on two of Dr. Fowler's questions. One, the liver is certainly distorted, and I have no difficulty whatsoever in visualizing its being flattened by the flattened diaphragm. [Second, I just happen to have a slide in my pocket at this time of an emphysematous lung at autopsy. This patient had a 30-liter maximal breathing capacity, and down at the bottom of the illustration you can see the diaphragm. I think you can see it is essentially hypertrophied.] In general, the diaphragms in obstructive emphysema are hypertrophied.

Dr. Fritts: I am delighted to hear Dr. Pratt's statement because this problem has puzzled us for a long time. When the diaphragm contracts, its total force of contraction (which is in the direction of attachment) can be resolved into two components: one which produces flaring of the ribs, and the other (inward) component which is exerted along the axis of the ribs laterally. In a child who has had a phrenic injury at birth, the diaphragm balloons "way up" into the chest and the flare on that side is accentuated, not reduced. Hence, it occurs to me that the force of the other inspiratory muscles in this situation adds a rotational component to that of the diaphragm. In the child with paralysis of the diaphragm there is no lateral component; hence the flare is accentuated. In the patient with emphysema, because of the attachment of the diaphragm, the inside contractural force goes into the restraining component. It seems then that, since the rib flare occurs in many patients with emphysema, the lower ribs move inwardly with inspiration. The diaphragm is probably operating, but its point of attachment is so different from the normal that the motion is inward.

Dr. Oderr: Dr. Goldenstall in the radiology department at Yale has recently developed a special kymogram to study the motion of the diaphragm. In normal subjects you get a nice smooth S-shaped curve, whereas in emphysema you get an abrupt inflection. When this becomes commonly used, we will learn a good deal more about the diaphragm.

Dr. Fowler: One thing which Goldenstall also uses is a method of getting a record of motion versus time. I have been waiting for a long time for the radiologists to do this rather than to carry the record in their heads as philosophy and then attempt to write it down.

Dr. Harold Lyons (Brooklyn, New York): We've been using this same radiographic method and, interestingly enough, Dr. Coates, we have also been studying pneumoperitoneum to see if there were any changes We do find appreciable changes in the motion of the diaphragm in the pattern which Dr. Oderr described. We have also turned our kymograph around and are getting some kymographic motions of the chest wall, too, which we think are also important though we have not analyzed them enough.

Dr. Radford: Our discussion has centered around the interrelationships between the chest wall movement and the lung movement, and I think this is a very pertinent discussion for an emphysema conference. Without going into too much detail, I would like to point out that the movement of the diaphragm, as the principal muscle of respiration, is converted in effect from a one-directional phase into a three-dimensional change in the lungs.

The phenomenon which Dr. Fritts described is, I believe, important because the diaphragm does cause both an anteroposterior and a lateral enlargement of the chest. Whether it is only localized in the lower ribs, as he said, or in the whole rib cage, as Campbell now believes, is a point which we cannot settle here. What I am emphasizing is that, as the lung moves downward, the hilus moves downward in the normal lung. This means then that the dimension from the apex to the hilum also increases, and thus the whole lung is being pulled down. Since the thorax is a conically shaped structure, this means that a dimensional change in the long axis of the lung can be converted into a dimensional change in the short axis or the lateral or anteroposterior dimension. I am sure that in emphysema this whole arrangement is completely upset because the diaphragm no longer has the same anatomic relationship. It would be quite interesting to know if the crucial point in emphysema (at which point dyspnea or some other clinical signs become significant) is the point at which the angle of attachment of the diaphragm converts the dimensional change of the thorax from one of expansion to one of contraction.

THE PHYSICS OF AIR FLOW IN EMPHYSEMA[1]

DONALD L. FRY

Introduction

The flow through any conduit system is determined to a first approximation by the pressure drop along the system and the dimensions of the system. In the lungs the dimensions of the conduit vary with the flow and the degree of lung inflation. Therefore, it is not surprising that experimental evidence from human subjects indicates that the bronchial pressure-flow relationships are different at different degrees of lung inflation (1–3).

Materials and Methods

A simple lung model from which an elementary mathematical pressure-flow-volume relationship may be derived may be seen in figure 87. It consists of an elastic air sac (A.S.) that ventilates to the atmosphere through an elastic tube consisting of two parts: an intrathoracic part (L.A.) and an extrathoracic part (U.A.). The intrathoracic part of the tube shall represent the lower airways and the extrathoracic part the upper airways. The thoracic cavity is represented by the cylindrical chamber fitted with a movable piston that will be the analogue of the diaphragm. The pressure in the cylinder is P_T, the intrathoracic pressure. At any given time P_T will be the difference between two pressure increments: the pressure increment P_L, required to maintain inflation of the elastic sac; and the pressure drop from alveolus to atmosphere, P_p, which is associated with the flow, Q. Thus,

$$P_T = P_p - P_L \qquad 1.$$

If, as shown in figure 87, the pressure drop in the lower airways (the intrathoracic part of the tube) is p_1 and that in the upper airways (the extrathoracic part of the tube) is p_2, then the total pressure drop (P_p) is given by

$$P_p = p_1 + p_2 \qquad 2.$$

and therefore

$$P_T = p_1 + p_2 - P_L \qquad 3.$$

The radius of the compliant intrathoracic part of the tube will vary with lateral pressure difference acting across its wall. Therefore, since the radius, flow, and pressure drop all vary, let us assume the most simple possible linear relationship between these variables: that the pressure drop, p_1, varies directly with the flow, Q, and inversely with the radius, R, at the oral end of the intrathoracic tube as given by

$$p_1 = \frac{K_1 Q}{R} \qquad 4.$$

where K_1 is a flow-resistance constant for the lower airways.[2]

The radius, R, will be determined by the pressure difference acting across the wall at that point. Since the pressure on the outside of the wall is the intrathoracic pressure, P_T, and that on the inside at the oral end of the intrathoracic tube is numerically equal to the pressure drop in the upper airways, p_2, the pressure difference at this point will be simply $P_T - p_2$ or $P_p - P_L - p_2$. Let us further assume that the bronchial compliance, K_2, is such that we can relate R to this transmural stress difference by

$$\begin{aligned} R &= R_0 - K_2(P_p - P_L - p_2) \\ &= R_0 + K_2(P_L + p_2 - P_p) \end{aligned} \qquad 5.$$

where R_0 is the resting radius of the tube. Substituting this into equation 4 for R gives

$$p_1 = \frac{K_1 Q}{R_0 + K_2(P_L + p_2 - P_p)} \qquad 6.$$

Let us now get P_L and p_2 in terms of the volume of the elastic airspace, V, and the flow, Q. The relationship of P_L to volume, V, is given by the conventional expression,

$$P_L = \frac{V}{C} \qquad 7.$$

where C is the lung parenchymal compliance and V is the volume to which the elastic airspace is inflated.

The pressure drop, p_2, in the upper airways will not be influenced by the intrathoracic pressure and therefore let us assume that p_2 is related to the flow, Q, by the simple relationship

$$p_2 = K_3 Q \qquad 8.$$

where K_3 is a flow-resistance constant for the upper airways. Substituting these latter two equations for P_L and p_2 into equation 6 and then substituting equations 6 and 8 into equation 2, the pressure-flow-volume equation for the model becomes

$$P_p = \frac{K_1 Q}{R_0 + \frac{K_2 V}{C} + K_2 K_3 Q - K_2 P_p} + K_3 Q \qquad 9.$$

[1] From the National Heart Institute, Bethesda, Maryland.

[2] A somewhat better but more complex approximation would be to let p_1 vary inversely with R^4. This, however, would further complicate and obscure the basic idea being presented.

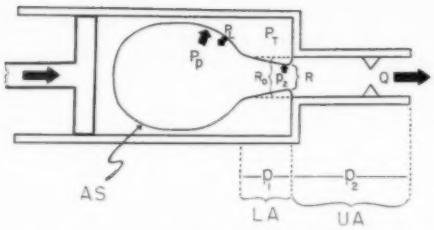

FIG. 87. A simple lung model during expiration.
AS = elastic air sac
LA = lower airways
UA = upper airways
$P_T = P_p - P_L$ = "intrathoracic" pressure
P_L = Pressure required to maintain inflation of air sac
$P_p = p_1 + p_2$ = total pressure drop from air sac to atmosphere
Q = flow
R_0 = resting radius
R = radius

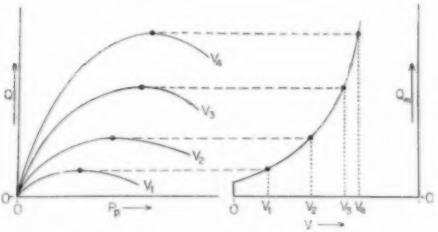

FIG. 88. The relationship of pressure-flow-curve maxima to the degree of lung inflation. On the left are a family of 4 isovolume expiratory pressure-flow curves.
P_p = airway pressure drop
Q = flow; V = inflation; Q_m = flow coordinate of maxima
$V_1 < V_2 < V_3 < V_4$

where P_p is the pressure drop along the entire tube, Q is the flow, V is the volume to which the elastic air sac is inflated, K_1 is a flow resistance constant for the lower airways, K_2 a flow resistance constant for the upper airways, R_0 the resting radius of the tube, K_2 the bronchial compliance, and C the lung parenchymal compliance.

Plots of expiratory pressure-flow curves, P_p versus Q, at various volumes, V, from equation 9 are shown schematically on the left of figure 88. These curves resemble the isovolume-pressure-flow curves previously shown from human subjects (1-3). It should be noted particularly that these curves have maxima, that is, on each curve there is a point where increased pressure applied to the lung is associated with a *decrease* in flow rather than an increase. Maxima may be thought of as points where the slope drawn to the curve becomes horizontal or zero. By the mathematical operation of differentiation, a formula for the slope at every point on an isovolume-pressure-flow curve may be derived from equation 9.

It follows from the preceding two statements that, if one sets the slope equal to zero in this formula, it will satisfy all the maxima on the isovolume P-F curves. Thus differentiating equation 9 implicitly with respect to P_p to get the slope formula and then setting the slope equal to zero gives:

$$P_p = \frac{R_0}{2K_2} + \frac{V}{2C} + K_2 Q \qquad 10.$$

We now have two simultaneous equations (10 and 9) satisfying the maxima. Therefore, substituting equation 10 into equation 9 to eliminate the pressure ordinate of the maxima, a relationship is obtained between the maximal achievable expiratory flow, Q_m, and the degree of lung inflation, V, for the system constants.

$$Q_m = \frac{1}{2K_1}\left[\frac{R_0^2}{2K_2} + \frac{R_0 V}{C} + \frac{K_2 V^2}{2C^2}\right] \qquad 11.$$

A plot of this relationship appears on the right of figure 88 as a solid line. The flow and volume coordinates of the maxima from the isovolume-pressure-flow curves on the left appear as solid circles on the maximal-expiratory-flow versus volume curve on the right.

COMMENT

Thus, we have a relationship between maximal expiratory flow, Q_m, and inflation, V, that has certain interesting and unique properties:

(*1*) It can be simply obtained by the measurement of Q_m and V.

(*2*) The relationship is independent of the upper airway resistance i.e., K_2 drops out of 11.

(*3*) The relationship is determined by the resting dimensions and physical properties of the intrathoracic airways, where most pulmonary disease states occur.

(*4*) By fitting equation 11 to an experimentally determined maximal flow versus volume curve, it should be possible to evaluate numerically certain combinations of the system constants in the equation and thereby obtain an estimate of the physical properties and resting dimensions of an unknown system by inference.

Although this mathematical model is entirely without rigor, it is extremely useful qualitatively in seeing the effect of varying the resting radius, R_0, the parenchymal compliance, C, the bronchial compliance, K_2, lower airway resistance, K_1, the upper airway resistance, K_2, on the pressure-flow-

volume relationship. Many clinical observations may be more easily explained by use of this device and the above constants, e.g., how certain drugs may alter K_2, C, or R_0; how helium may alter K_1 and K_3; how pursed lips beneficially alter the breathing pattern in emphysema; how resistance measurements vary with inflation and effort; and how the mechanism of the various clinical ventilatory tests operates.

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General Discussion

Lt. Col. G. C. Clementson (Denver, Colorado): I will confine my remarks to an area in which at least, if I'm not more expert, I am familiar with the terms involved. The work that Dr. Fry has done is the type of approach we use quite effectively in both aerodynamics and hydrodynamics. We use not only mathematical models but also physical models and the interplay between the two of them. I will use this analogy as I go along. Involved in this approach is an extremely difficult problem. Even in systems in which there are rigid boundaries, it is still pretty tough, for when you build a mathematical model you may end up with a partial differential equation, which is highly nonlinear, and Stokes equations for which, except in very special cases for unusual boundaries, you cannot find solutions. We are forced also to resort to the use of physical models as well as mathematical models. We are able to obtain from these models a field for trends and interrelationships between the variables, especially when some of the variables cannot be independently changed.

For example, when you change one of them, by necessity you change others. Normally, the way you proceed is to start with a mathematical model, and on the basis of this go ahead and build a physical model and then use this to try to make the best design of the prototype that we are speaking of, and we are speaking of aerodynamics in the design of an airplane. Of course our considerations are primarily economic. Airplanes are very expensive, and when we build them we like to have a minimal amount of modification involved before we have a satisfactory airplane. As a result we start out with a mathematical model and, on the basis of that, we build a physical model which we put in a wind tunnel; in the wind tunnel we conduct experiments and find certain modifications to be necessary on the basis of these experiments. Then we go ahead and build the prototype. After we build the prototype we conduct flight tests and, on the basis of the flight tests, we find further modifications necessary. Eventually we hope that we end up with a satisfactorily flying airplane. All the time this is a continuous process with interplay back and forth. The end objective is not in itself the prototype but it's worth a lot of money in the future to know that we have a good system by which we can use not only the mathematical model but the physical model to predict the performance of the prototype. So we continually go back and modify our models and our concepts with respect to building not only the physical but also the analytic or mathematical model.

I think this situation exists here. What Dr. Fry has done, I think, is to create a simple mathematical model as he has built a physical model, and the correlation is quite good. There is an important question, though, as to the interrelationship between the physical model that he built and the prototype of the human being of which you would like the model to be representative. This leads us to the point, and that is that the next step is the problem of instrumentation. Of course yours is much more difficult than mine, for I am sure that your subject is much more difficult to instrument and to measure. Nevertheless, this process of instrumentation is the place where the mathematical model becomes of extreme importance because it permits you to use dependent relationships between the variables to get at one of the particular variables that you may not be able to measure directly. I think that this is the big advantage of the step that Dr. Fry has taken here. I don't think this approach, in itself, will tell you where the disease came from, but it will certainly tell you a lot more about the normal functioning of the lung; and on the basis of the normal functioning you probably can predict what has gone wrong, or at least find out what has gone wrong and thereby arrive at some way of correcting it.

Dr. Wesley Childs (Albuquerque, New Mexico): We have been doing some work on surgical treatment in emphysema. We came to the conclusion that, if we could reduce the over-all size of the lung contained in the thorax, we might get rid of some of the troubles that obviously do occur. In this model (figure 89), it may be seen that, as the plunger is drawn up slowly, the negative pres-

FIG. 89. Model of an emphysematous lung (balloon) attached to an easily collapsible tracheobronchial tree (glass tube and thin rubber tubing) in a thorax (large glass tube with plunger).

sure can make the balloon fill. But, as you all know, when the lung of a person with emphysema becomes overdistended, the subject does not get the air out. When I suddenly push the plunger in, I think you will see that there is an immediate tendency for this small passage of Penrose drain (analogous to the terminal bronchioles) to collapse. There is a glass tube connecting the Penrose drain to the neck of the balloon, so there is no question of the collapse of the junction before the Penrose drain collapses. This balloon can be expanded and contracted easily if it is done slowly. But, if it is done rapidly, the balloon will not deflate. This might explain some of the pathologic unknowns which were spoken of yesterday. If the bronchus is long or if the lung simply becomes voluminous and outside pressure is then applied to the smaller division of the bronchus, one could in essence have emphysema which would result from no organic disease of the alveoli.

There is some evidence that this does occur. I don't think we can call it really good evidence, but a few of our patients who have had these operations have developed spontaneous pneumothorax on the *unoperated* side during the postoperative period. At first we could not recognize it by physical findings for the reason that these people developed marked wheezes. Our explanation was that excessive pressure on the outside had produced this type of phenomenon. Another line of evidence which leads to the same conclusion is that, if careful attention is paid to the stories of some of these emphysematous patients, it will be found that they didn't develop their wheezing until late in the course of the disease. A third reason that we think this may develop is based on the fact that the bullae of some patients can be made to inflate and deflate at the operating table, but only after the lung is removed from the thorax. We think this is due to kinking of the bronchi. This kinking or folding over is not man-made. It is actually present, and its cause must be found before the lung is removed from the thorax or greatly disturbed, if it is to be found. It would seem that everything distal to this foldover process becomes a bleb.

DR. GAENSLER: We have had a problem in trying to teach medical students what is the dynamic difficulty of breathing in the patient with emphysema. We have a very simple model, of which we have some 20 or 30, that the students can use at once. This is merely a glass tube with a rubber stopper on either side and surgical rubber drain inside it. When the student breathes through the glass tube the pressure of the mouth is transmitted to the outside of the rubber drain so that it collapses; when he passes air back out, the pressure becomes negative and the drain has the tendency to become larger. With this model many of the things which we have discussed in emphysema can be reproduced. It can be shown that the student's functional residual capacity rises while he is breathing through this thing. It may be observed

that his maximal breathing capacity diminishes perhaps to about 10 per cent of what it was and that he immediately assumes an emphysema pattern of breathing.

DR. DAVID CUGELL (Chicago, Illinois): With the image amplifier we have been able to record simultaneously diaphragmatic motion and pneumotachographic tracings. This has tremendous possibilities in analyzing diaphragmatic motion in a variety of chest diseases. The maximal rate of air flow normally occurs at the onset of diaphragmatic motion either when it's going up or when it's going down. We have pictures of a patient with severe emphysema with paradoxic movement, showing that the maximal expiratory flow rate occurs at the onset of diaphragmatic motion when the diaphragm goes down instead of up. The film is analyzed strip by strip, measuring exactly how far it moves for each air volume which is expressed. Dr. Childs' model was beautiful, but he made one statement with which I would disagree. He said that emphysematous patients have learned that to expire they have to grunt, and this is not our experience. They breathe out slowly and they have learned this, I am quite sure, without understanding it.

DR. DAYMAN: Much of what has been said is plainly visible to the clinician. You can fluoroscope the patient and see the evidence that the airways collapse; you can put a dead lung in a pump and observe it too. It is independent of humoral and neural control. It is a straight mechanical phenomenon. We use a pragmatic approach and investigate the relations between flow and volume by actual test. To ensure that we get what Dr. Fry calls maximal flow (I call it critical flow), we have the patients cough and then produce a series of coughs. You can identify the place in the flow tracing where the patient has reached an equilibrium between bronchial diameter and the dynamic pressure of flow.

DR. JERE MEAD (Boston, Massachusetts): First, I want to disabuse any nonphysiologists of the thought that the physiologists are thoroughly *"with"* a presentation such as Don Fry's in terms of understanding it. Right at the moment we don't, but we greatly respect Dr. Fry's work and I personally think it is a tremendous advance. Recall Dr. Fry's graph that showed maximal expiratory flow on the ordinate (figure 88). It is my opinion that, if none of you understood any other thing on that figure than that particular ordinate, the letter $\dot{V}_m$, you have a very useful concept, which is a new one, to take with you.

Now I will say what the ordinate is again, to refresh you memory. The general concept is that at a given lung volume there is a flow velocity above which you just can't go in emphysema, or even in a normal person within certain limits. This is a new and useful concept that has added to all the previous knowledge about respiratory trapping. If you think about this concept, you'll find it useful in a great many applied clinical problems.

Second, for years clinical physiologists have been able to make good use of the timed vital capacity. Now an electrical engineer would be amazed by this circumstance because the physiologist is using a performance measurement to assess a mechanical property. The patient is told to try hard to breathe out, and a certain result is obtained. If the lungs worked like any other respectable mechanical device, the result would relate to the force applied. But notice here that the result is determined by a mechanical effect and, for this reason, a simple test is useful.

DR. FILLEY: Dr. Mead has touched on something very important. He said the engineer would be amazed at the fact that more force produces less effect. But the biologic engineer would not be at all amazed, if he were a good engineer, because some biologic mechanisms work well only under appropriate conditions. In general, the normality, for practical purposes, of a biologic mechanical system can be best deduced by considering what has been written in Barcroft's book, *Features in the Architecture of Physiological Function*, in the chapter called "The Principle of Maximal Activity." You cannot tell the difference between normal and abnormal function unless you stress this function to some maximum. This is the basis of the fast vital capacity test and of many of the tests which we hope will have some bearing, not only in diagnosis, but in definition of this disease.

DR. FOWLER: One thing has not been mentioned although it may have been in Dr. Fry's equation. I had one of my engineer friends play with some of these concepts at one time, using an acoustic equation, and it became quite apparent (which it hadn't been to me before) that the stiffness of the lung and the airway resistance involve the compliance of the stuff we breathe. All this means is that the human lung is constructed, in terms of its physical properties, to breathe air and not molasses.

THE CIRCULATORY DYNAMICS IN PULMONARY EMPHYSEMA DURING TREADMILL EXERCISE[1]

S. G. BLOUNT, JR., AND J. T. REEVES

A technique has been developed whereby subjects have been studied by pulmonary arterial catheterization during treadmill walking. We have found that this technique is safe and that it provides constant and easily regulated exercise in the upright posture.

Sixteen patients with mild or severe diffuse pulmonary emphysema have been studied at rest and during upright exercise. All patients were evaluated clinically and by ventilatory and carbon monoxide studies. Pulmonary emphysema was the primary or only disease present, and no patient was in heart failure at the time of the study.

The results were compared to those of normal subjects and of other patients with pulmonary emphysema from this and other laboratories. In our 16 subjects the resting cardiac output was in the low normal range. With exercise, the cardiac output tended to be lower than normal for the work performed and the oxygen taken up. It should be stated that this study compares the performance of elderly men during upright exercise with that of young men during supine exercise. Studies of normal subjects exercising in the upright posture are in progress at this time.

The mean exercise pulmonary arterial pressures ranged from 36 to 105 mm. of mercury, and the total pulmonary resistance during exercise ranged from 610 to 2,500 dynes-sec-cm^{-5}-m^2. By determining oxygen uptake and the oxygen content of arterial and mixed venous blood at frequent intervals, it was found that a steady state existed in these patients after about four minutes of exercise.

Studies on the patients with emphysema at rest and during supine exercise have shown that the cardiac output tends to be low and the pulmonary arterial pressure and resistance tend to be high. Although an inverse relationship between the maximal breathing capacity and the calculated pulmonary resistance was shown, it was apparent that emphysema is a disease in which the relative severity of obstruction to gas flow and obstruction to blood flow vary from patient to patient.

[1] From the Department of Medicine, University of Colorado School of Medicine, Denver, Colorado.

General Discussion

DR. HECHT: I am delighted to find that Dr. Blount's findings are the ones I expected. The most important contribution here perhaps is the handling of exercise response by a treadmill technique. I think that we are learning more and more that the resting analysis of the vascular system really is not what we want. At least I don't rest most of the time, and I doubt that anyone here in this room does. Really what's going on is not properly reflected in most instances in a completely basal patient. So I think this is a very important demonstration of how such studies ought to be carried out.

The problem, of course, is why do these people go into heart failure. This is something that is puzzling because you can't say that any individual factor is in itself sufficient to overload the heart and cause right heart failure. I would like to say that "cor pulmonale" is a wastepaper term and that we should drop it and call this simply the "emphysema heart." The arterial desaturation, if such is present, does not give you heart failure.

The problem of pulmonary hypertension has always been brought into play, and it has been said that excessive pulmonary hypertension is the reason for overloading the heart. Now this is true when the pressure is really high, but unfortunately there is another kind of cor pulmonale, namely, pulmonary hypertensive heart disease. This has quite a different picture from the emphysema heart, both from the clinical point of view and from the point of view of physiologic study. Although some cases of emphysema heart may well go into an overload type of failure, it might be worth while to think of these two events in two separate groups that naturally will merge at some points.

I wasn't too happy yesterday when Dr. Liebow threw everything into the same category, including excessive pulmonary hypertension and thrombosis, and so on. The third factor making up the triad in the emphysema heart is the presence of polycythemia, which is related to arterial desaturation, if such is present. Polycythemia in the resting state does not seem to alter the hemodynamic function very much. Fortunately, here we have a controlled experiment in subjects with polycythemia vera who show some disturbance in their respiratory functions, as you know, but not a very consistent one, and they show in general a

quite normal resting cardiovascular adjustment. When these people are exercised they show a rather interesting fixation of their cardiac output. A rise in pressure is observed, at least in the very few cases that we had an opportunity to study.

We are left with the question unanswered as to why the heart fails in emphysema. I can't help suspect that these people have a myocardial factor, namely, heart disease (let us say) on an arteriosclerotic basis, and that this myocardial factor makes them go into failure. You are all familiar with the relatively early occurrence of heart failure in the face of relatively mild pulmonary disease. On the other hand, particularly in the younger people, there may be severe pulmonary malfunction and insufficiency without the occurrence of heart failure. I then say that, though the output may be normal or low normal, as Dr. Blount has shown, perhaps it isn't as low as might be seen in a hypertensive patient in failure or in a patient with pulmonary stenosis in failure, or situations of that sort. But it isn't high enough for what it's supposed to do to maintain internal oxygen transport, so that there may be evidence of a low output syndrome, at least a relatively low output syndrome.

The normal lung is a peculiar thing not only for you but also for us. And the most peculiar things that we run into are the vascular pathways and how we should label them. There are two systems of flow and pressure relationships, the bronchial one that Dr. Fry talked about and the vascular one that Dr. Blount talked about. Now when you try to see what kind of vascular pathways there are in the lung you discover some peculiar data. We find that dye curves based on simultaneous sampling from the pulmonary artery (after injection of a dye into the peripheral vein) and from the femoral artery show virtually the same shape. The pulmonary and femoral arteries are sampled simultaneously by a device that samples both places at the same rate. We use a pump affair so that we can be sure that each curve is drawn with the same speed through a freely flowing pulmonary and femoral artery.

When this is done, it is very surprising to see that the curve is little changed by dye passage through the lung, particularly with respect to the log of the down slope. This means that once the dye is mixed it passes through the pulmonary circulation without being particularly altered. This is very odd and makes it most difficult for those who try to calculate pulmonary blood volumes from dye curves.

With this particular technique this can only be reproduced in a model if a single connection is made between the right ventricle and the left ventricle. This suggests that, under ordinary circumstances, in the lungs all major passages are similar in volume as well as in length. I should say that, using our method, there is no difference between needle sampling and catheter sampling. In order to repeat this result, exactly the same technique must be used, and it isn't going to be very helpful if somebody says "We can't find it" and uses a totally different technique.

In severe emphysema there is very little change again; and we have seen this in a number of cases. The difference between the mean circulation time and the mean early appearance times is the same in the two curves so that, even though very severe emphysema is present, there is no striking difference between the right-sided curve and the left-sided curve.

Dr. Fritts tells me that this peculiar behavior does not obtain if severe destructive lung disease is present, with the holes mentioned by Dr. Fishman, and that under those circumstances, as you might expect, the passages through the lung are different in one section of the lung from those in the other. I believe this is where Dr. Liebow's beautiful studies also fit in. But in the ordinary type, I think you'd still have to consider that flow to the lungs is relatively similar in similar areas.

Finally, I'd like to say that the capillary net that Dr. Loosli showed has, I think, a built-in mechanism for the peculiar changes that might occur. The capillaries here act the same way as they do in the rest of the body and have the mechanism for shunting blood, for changing the diffusion capacity during exercise and so on, "built in" by the simple mechanism for capillary closure. Now I don't want to go into the problem of critical closing pressure, but I think we are standing now at the threshold of an era when these peripheral vascular approaches are to be applied to the pulmonary circulation in the case of emphysema.

DR. WILLIAMS: I have a couple of questions for Dr. Blount. We have studied about 10 patients with emphysema during supine exercise and found increases in cardiac output and pressures similar to those that you have described, but we're worried about the fact that the total pulmonary resistance increases and we wonder how much of this may be due to the fact that the intrapleural pressure may increase. We are beginning now to incorporate this measurement into the studies, as I believe you are, and are concerned that the mechanical increase of pressure in the thoracic cage may be what we're looking at.

The other question that I would like to ask you is your definition of emphysema, because one of your patients, though the maximal breathing capacity was reduced, had a normal lung volume, a normal MMF, and only moderate reduction of

the diffusing capacity. What are the criteria for emphysema in this patient?

DR. BLOUNT: With the first question I certainly agree, as far as intrapleural pressure is concerned, that we certainly need to know this and realize this. As you know, we are instituting this measurement in the near future. As to the criteria for the emphysema of that patient, I'm just going to pass that right over to Dr. Filley.

DR. FILLEY: Clinically the man has very early emphysema. We have found that such patients who on clinical grounds have early emphysema may have very little abnormality in objective measurable phenomena based on function tests but that, if you follow them a year later or so (or less, in fact), these changes in objective measurements may be very profound. I think the natural history of emphysema is still to be worked out from the earliest to the more advanced and more easily diagnosed condition.

DR. BLOUNT: We had only one patient with mild disease in our study.

DR. BATES: One of the really important issues raised by Dr. Blount's paper is one he didn't mention. If the diffusing capacity as measured by Filley's method is the best indicator we have of the normality of the pulmonary vascular bed, the reduction in diffusing capacity on exercise should correlate most closely with the increased pulmonary arterial pressure. Does it?

DR. FILLEY: We have not done statistical analysis on the first 10 or even 16 patients because this did not seem necessary. The best correlation is between the diffusing capacity and, not the pressure, but the pulmonary vascular resistance. The patients with the highest pulmonary vascular resistance during treadmill exercise in general are those with the lowest carbon monoxide diffusing capacity.

DR. FISHMAN: Dr. Filley answered my question, at least in part, because I'm not quite sure that Dr. Bates' original premise is the right one, that the diffusing capacity is the measure that we're really looking for that indicates the state of the pulmonary vascular tree. We have data similar to those that Dr. Filley just mentioned, at rest and during exercise, studying carbon monoxide diffusing capacity versus pulmonary arterial pressure, and in general this is right. There is a good relationship between a low diffusing capacity and a high pulmonary arterial pressure, but it is not an invariable relationship, at least in our hands.

Many people have found high cardiac output in emphysema at rest. I am not surprised, though, that Dr. Blount in his series of 10 or 16 patients did not find it, because I think it's a matter of the number of patients you study and in what stage of disease you happen to catch them, because the early studies were done on severely hypoxic subjects. I remember studying some of those myself, done with the same technique. When saturations are as low as 60 and 70 per cent at rest, even though the patient is in a hospital with bronchitis that you can't detect, he's still got emphysema. He still can be studied, he can still be exercised, and in that particular patient you may find a high cardiac output at rest. If you study him a year later when he's been to Denver and he's fully recovered, the saturation may have reversed itself. So I think one important point is "What is the saturation of the patient and his clinical state at the time of study?" I don't want to belabor this, but I am surprised that the patients, regardless of their level of initial cardiac output, fail to increase their cardiac output normally, because in both normal subjects and patients with emphysema it can be shown that a young patient who has never been troubled with heart failure shows an increase between 700 and 1,000 ml. of blood flow per 100 cc. in oxygen uptake. Some of your patients (I think I would reaffirm Dr. Hecht's thought here) may have a myocardial component which isn't disclosed by this type of study.

DR. BLOUNT: I think it's apparently true, when you're dealing with any patient between the ages of forty and sixty-five, that some may very well have a myocardial factor that certainly is not evident. As far as the high cardiac output is concerned, this is always brought up. We're still looking for that one with the high output. I think that probably some of the patients with bronchitis whom you studied earlier did have outputs that came down when they were given penicillin and their temperature metabolisms were lowered.

THE ENERGY COST AND CONTROL OF BREATHING IN PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA[1, 2]

HARRY W. FRITTS, JR.

The diminished ventilatory response of patients with chronic pulmonary emphysema to the inhalation of small concentrations of carbon dioxide has been generally attributed to one of two factors: (*a*) a diminished sensitivity of the respiratory center to the hypercapneic stimulus, or (*b*) the increased work required to ventilate the lungs.

To determine the individual importance of these two factors, the minute volume of ventilation ($\dot{V}_E$), the arterial blood carbon dioxide tension (Pa_{CO_2}), and the oxygen uptake ($\dot{V}_{O_2}$) were measured while normal subjects and patients with emphysema breathed various concentrations of carbon dioxide. On the assumption that the change in Pa_{CO_2} was proportional to the change in stimulus delivered to the center, the combined response of the center and the muscles was judged by relating the increment in the oxygen cost of breathing to the increment in Pa_{CO_2}. The role of the work of breathing was concomitantly evaluated by relating the increment in ventilation to the increment in energy consumed.

When the results in 8 normal subjects were compared with those obtained in 9 patients with chronic pulmonary emphysema, it was found that the combined performance of the center and the muscles in the two groups was much the same. But in the patients with emphysema, the behavior of the lungs and chest wall was different. Here, the increment in ventilation realized per unit of energy expended was clearly reduced.

In a separate study, the effect of 50 per cent oxygen on the response to carbon dioxide was studied. The effect was negligible in 8 patients with emphysema in whom the resting Pa_{CO_2} was normal. By way of contrast, 50 per cent oxygen regularly reduced the resting ventilation in 8 other patients who exhibited an elevated Pa_{CO_2} at rest. However, each patient in this second group showed approximately the same response when 3 per cent carbon dioxide was added to the 50 per cent oxygen as he did when 3 per cent carbon dioxide was added to atmospheric air.

In summary, it appears that the increased work of breathing is an important factor in reducing the response to inhaled carbon dioxide in patients with emphysema. Furthermore, 50 per cent oxygen may reduce the ventilation in patients with a moderate degree of carbon dioxide retention but, in terms of increments, the response to 3 per cent carbon dioxide is about the same in 50 per cent oxygen as it is in atmospheric air.

General Discussion

Further comments by Dr. Fritts: I would like now to speak less formally on the relevance of these observations to the control of ventilation as a whole. Dr. Fowler has already sounded the theme that I should like to emphasize. I'm not certain that these experiments take into account the basic design of the respiratory apparatus. Dr. Fowler said we have to look at all the variables, all the factors that may influence the respiratory center. And admittedly we have considered this as a system in which we put in carbon dioxide and get out ventilation. It's stripped of the effects of the afferents which he has talked about. Dr. Grodins and his associates, Dr. Gray being one of them, have already published an admirable analysis of the behavior of the normal respiratory apparatus as a closed cycle system, and without question that should be the approach used in experiments such as these. We have thought considerably about this, however, and, if we had taken into account feedback, I think that the absolute numbers might have been changed; but I don't believe it would have had a gross effect on the comparison among the different groups.

The last point that I want to make concerns the matter of randomization of the sequence in which various gas mixtures are breathed. Apart from pleasing statisticians because it's a good way to set up experiments, I think it's important because it minimizes the effect of fatigue. Last year a number of us in the laboratory breathed through small obstructions, and you only have to do that for a little while to realize how tired a man with chronic obstruction must be. To find out how much fatigue could affect our observations, we took 10 normal subjects, allowed them to train a bit, and then

[1] From the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York.

[2] Brief summary of paper by Richards, D. W., Fritts, H. W., Jr., and Davis, A. L.: Tr. A. Am. Physicians 1958, *71*, 142.

measured how much ventilation they could maintain for sixteen minutes. By this I mean the maximal ventilation they could hold steadily for the sixteen-minute period. For most of us who took part in the study, this was exhausting exercise. In these 10 normal subjects who breathed as hard as they could at the same minute volume for sixteen minutes and expressed in terms of the maximal breathing capacity, on the average, the best they could maintain was 56 per cent. There was a fair range from 51 to 71. We then took 8 patients with emphysema and we immediately had to change our protocol. These patients, even though they were intelligent and tried to pace themselves, could not really maintain a set value of ventilation for sixteen minutes. So we had to settle on six minutes. These patients were able to maintain an average of 60 per cent of their maximal breathing capacity. One man maintained 95, for no reason that we could see. The rest of the values fell below 65 per cent.

In summary then, we think that the effort of breathing is quite important in reducing the response to carbon dioxide. For some reason, patients who retained carbon dioxide, or at least the patients that we saw, behaved differently when oxygen was breathed. Finally, we're aware that there are a great number of other factors that must have an effect on this response, and I believe that fatigue is probably an important one of these.

Dr. Filley: This paper shows that pulmonary physiology is rapidly expanding into areas where basic concepts from the field of thermodynamics are going to be used more and more. There seems to be considerable difference between what Dr. Fowler mentioned as physical work and physiologic work. Possibly, for clarity or simplicity or for purposes of communication, Dr. Fritts equated the word "effort" with the ordinate of oxygen consumption. Oxygen consumption has the dimensions of power; effort, so far as I can make out, seems to be most closely related to impulse, which can be defined by the physicists as the rate of change of momentum. These are difficult concepts. I'd just like to go on record as saying that eventually the dimensions of what we are discussing, both physical and physiologic, must be taken into account.

Dr. Reuben Cherniack (Winnipeg, Manitoba, Canada): We have been doing work along the same lines as Dr. Fritts, fortunately or unfortunately using an entirely different technique, and getting the same results. We find, too, that you cannot relate a change in carbon dioxide tension to a change in ventilation because of the inefficiency of the different processes you're measuring. However, I'm a little worried about even using oxygen consumption as a measure of response when comparing normal to emphysematous patients. And the reason I say that is that I think the response to a given carbon dioxide stimulus is the total work that results in response to the stimulus. From our studies it is very suggestive that there is a difference between normal and emphysematous subjects, as far as the efficiency of the respiratory process is concerned. I realize that Dr. Fritts has found that there is no difference. Our studies use a little different technique. We find a distinct difference between normal and emphysematous subjects in terms of efficiency. However, I don't know what this has to do with sensitivity and, if we're talking about definitions, I'd like to know a definition of sensitivity of the respiratory center.

To add to Dr. Fritts' second experiment on the effect of oxygen, we've been tackling this big problem. When we first set out to say that there was no change in sensitivity of the respiratory center, it was very difficult to explain why, when emphysematous subjects breathed oxygen, their carbon dioxide tensions went up. So we took a group of normal subjects and had them breathing through obstructions and breathing hypoxic and hypercapnic mixtures. In essence we had then an individual with obstruction, hypoxia, and hypercapnia—hypoxia at a level of around 40 mm. of mercury, and carbon dioxide retention varying between 45 to 50 mm. of mercury. We did this by having the subjects breathe through dead space and then adding a hypoxic mixture. Then instead of using the hypoxic mixture we turned the individual into 100 per cent oxygen. And in these subjects carbon dioxide tensions rose from 45 to 65. There was a marked drop in ventilation, even in these normal subjects, with a tremendous drop in respiratory rate, and they breathed along merrily at a carbon dioxide tension of 65, so there certainly is something complex about the control. With what limited work we've done since, I'm inclined to believe that there is a relationship between the oxygen tension and the comfort of the patient and how much work he will do.

Dr. Coates: There is evidence that under certain circumstances a high carbon dioxide tension will diminish the ventilatory response. Young men exposed for considerable periods of time to a carbon dioxide enriched atmosphere have a ventilatory response which is definitely diminished during this period of exposure. Furthermore, I believe that Dr. Whittenberger has described a patient with emphysema with hypercapnia whose ventilatory response was considerably diminished with the inhalation of carbon dioxide and in whom this abnormal response reverted toward normal after use of a Drinker respirator.

A second item related to the point that Dr. Fritts made about arterial oxygen saturation in

relation to the ventilatory response. We've been interested in this problem also and in people with chronic hypoxia due to causes other than those associated with impaired ventilation. For instance, in congenital heart disease, we haven't been able to demonstrate any reduction in ventilation when the subjects are given 100 per cent oxygen to breathe.

DR. BATES: One question, since we have so many people here who exercise patients with emphysema. Did anybody present, studying patients with emphysema during exercise and trying to observe the efficiency of ventilation in terms of the plasma carbon dioxide and plasma oxygen in the blood at different respiratory rates, make these patients breathe slowly and deeply, measure the work of breathing, and then compare the results with those found during spontaneous breathing?

DR. S. M. TENNEY (Hanover, New Hampshire): The question Dr. Bates raises is a very intriguing one to me. Although we have not studied this problem in emphysema, I think we have some measurements that are pertinent. A normal subject, if driven to severe muscular exercise, approaches a limit beyond which his ventilatory response to inspired carbon dioxide is minimal and resembles that of patients with emphysema. There is also a very sharp point, as minute volume increases with increasingly heavy exercise, at which normal subjects change their respiratory frequency. The assumption has often been made that the human organism seeks optimal values for respiratory work. If this were true, then one would expect, I think, to see a different choice of respiratory frequency at comparable minute volumes, if in one case respiratory work were diminished. For instance, since at high minute volumes turbulent flow becomes a prominent factor, the substitution of a less dense gas than room air should alter respiratory work and presumably frequency.

We have thoroughly studied one subject, a superb athlete, who can drive himself over prolonged periods of severe degrees of muscular work. We have found two things of interest: the first, that he reached a point at which he did not further increase his minute volume but instead kept it relatively constant and by choice conserved carbon dioxide. During very heavy work he retained carbon dioxide up to levels of 60 mm. of mercury in the alveolar air. Second, if at this point the inspired mixture was switched from room air to 21 per cent oxygen and helium, the ventilation volume suddenly increased. Of course the maximal breathing capacity when breathing helium is larger than that when breathing air for almost all subjects. If you compute the increased minute volume which he now achieved as per cent of his helium maximal breathing capacity, it is found that he more nearly approaches the limiting value when breathing helium than when breathing air. The surprising thing, however, was that he didn't change his respiratory frequency.

What is quite clear is that a choice had to be made at some point when breathing each gas. This involved answering the question whether it was to his advantage to increase further the amount of air flow into the lung, despite a need for more carbon dioxide elimination and oxygen uptake. There is a critical ventilation beyond which the metabolic need of the ventilatory musculature is so excessive that the rest of the body may actually be deprived of further available oxygen. The choice is an important one since most of the energy consumed is needed by the skeletal muscles of locomotion during running. The critical ventilation should be higher when breathing helium than when breathing air since the work of breathing is less. We have made measurements of ventilatory work with controlled respiratory frequency at 10, 20, and 30 breaths per minute at rest and then compared the subject's choice of respiratory frequency at 50, 100, and 150 meters per minute of muscular exercise. The point at which he makes a choice does appear to be at a physiologic optimum when all of the curves of ventilatory work are compared. It is of interest that he always told us, without any prompting, that, as soon as he was switched into the oxygen-helium mixture—even during exhausting muscular exercise—he had the feeling that he had achieved a "second wind." The "second wind" is a rather mysterious symptom and at least one intuitive concept of what accounted for this subject's sensation was that there was now more oxygenated blood available to the extremities. I would suggest that maybe patients with emphysema at much lower workloads would do something similar.

DR. HOUSTON: One of the observations that probably doesn't have much bearing on emphysema, except that it relates to the fluctuations of the stimuli to breathe, comes from acclimatization to high altitude; it is a fact that normal subjects will begin to have Cheyne - Stokes breathing throughout their period of acclimatization. Even here in Aspen, if you look around at some of the natives, and if you observe it after you have been here for a while, you will notice that on some days or nights very definite Cheyne-Stokes breathing will be present and at other times it will not be present.

DR. FILLEY: I would like to tie Dr. Tenney's work into the problem of emphysema. It's an interesting question whether the emphysematous person "chooses" the optimal rate at which he breathes. We have been interested in this and have

produced another rate by teaching these people to breathe at different rates under the direction of a physical therapy department. We have now studied some 20 patients before and after they have learned to breathe at the new rate. It is markedly different from the way they used to breathe, coming down from an average of 26 to an average of 18 breaths per minute at moderate exercise. These patients will report subjective improvement in ability to climb stairs, with less dyspnea; they also seem to be able to reduce the total minute volume and perhaps the work—this has not been measured—and still maintain normal arterial blood gases.

DR. GAENSLER: We have approached this work of breathing in emphysema a little differently in that we've tried to work with resistance breathing and, for reasons that I do not understand, the oxygen cost of breathing is much more difficult to measure during extremely severe resistance breathing when an enormous increase in oxygen uptake would be expected. One thing we have noticed is that normal subjects indeed seem to choose a rate which makes it possible for them to breathe through an extremely severe and variable resistance, such as the kind that I drew on the board this morning. For example, if you allow their respiratory rate, which is normally perhaps 16 or 14, to drop down to 7 or 8, they manage, without carbon dioxide retention; but, if you have them breathe to a metronome at their previous rate, that is 14 or 16, then over the course of fifteen minutes they will develop very marked carbon dioxide retention. Another factor is the so-called "sensitivity of the respiratory center." If you have an individual on such a high resistance valve and you give him carbon dioxide to breathe, absolutely nothing happens to ventilation. The only thing that happens, of course, is that his carbon dioxide goes up. We've been interested in this, particularly in regard to positive pressure breathing, to aid the patient who is about to die of respiratory failure. We find that many of these patients, if they are just barely getting along, somehow must be choosing their rate in a fashion which makes them survive. Because, if you give them a positive pressure breathing device that allows them to continue at their rate—in other words, if during inspiration there is sufficient flow so that they can develop very high peaks of inspiratory flow—they will tolerate this machine, in fact might be helped by it. On the other hand, if this machine is incapable of giving them a sufficient inspiratory flow so that they have to change their rate of respiration, the machine within two or three minutes becomes entirely intolerable to them and they will tear it off their faces.

DR. BATES: Ward Fowler made an original observation about the importance of the afferent stimulus to the respiratory center. One of the main differences between Roger Bannister and myself—there are others—is that on exhausting work he has trained himself to exert conscious control of respiratory rate, and I haven't. It suggests strongly that the respiratory center is not of itself optimally efficient in choosing rate. Anyone who looks at emphysematous lungs will agree that it is inconceivable that such damaged organs can send normal afferent impulses to the respiratory center, whatever be the nature of the destruction. That's Ward's point about the abnormal stimuli outputs, irrespective of gases.

DR. FISHMAN: In all this complex array of presentation, I would just like to emphasize one point that Dr. Coates made. There are many clinical observations and observations on normal people which indicate that the respiratory center, be it diffuse or localized, is impaired in its response to carbon dioxide if a person lives in an environment of carbon dioxide. The experiments of Whittenberger that you mentioned are on diseased people, but the experiments of Otis were on people who lived in atmospheres high in carbon dioxide; and the experiments of Schaefer were also on normal subjects who came out of submarines where the carbon dioxide concentration rises. There seems to be no question that chronic exposure to carbon dioxide reduces sensitivity to it.

I also would like to point out that there is, without any question, a loss of carbon dioxide sensitivity in patients who have carbon dioxide retention and are put in an oxygen tent. I think we're ducking a little bit the question of sensitivity. I wouldn't like to boil it down to afferent or efferent impulses, but nonetheless it is quite striking and must reflect some loss of sensitivity or some controlling mechanism if a man who is put into an oxygen tent can build up a carbon dioxide 40 or even 50 mm. above his initial level. So I think we shouldn't sell short the concept of sensitivity loss, no matter how carbon dioxide retention is first initiated.

DR. MEAD: In terms of rates of breathing in emphysema and equating them to optima, we must take into consideration the influence of rate on distribution of ventilation and blood flow as an important additional optimum of energy effort. I think that the problem is extremely complex and that one cannot deal properly with optimal frequency in emphysema without including considerations of distribution.

DR. FRITTS: My use of the word "effort" was out of context and wrong. I meant the energy utilized by the muscles, measured in terms of the

extra oxygen they consumed. Second, I agree with Dr. Cherniack that the energy cost of breathing is not the ideal way to study this problem. The man who sinks an electrode into the reticular substance may very well demonstrate the ignorance of us all. We have found that the amount of mechanical work, the product of pressure times volume change, exerted on the lungs is the same fraction of the total energy which the bodies of both normal and emphysematous patients consume.

In reply to Dr. Coates, I would have to know what you mean by response and whether or not the plasma carbon dioxide of the blood was measured or whether these were just different inspired mixtures, which I think is not really a good criterion to use.

In reply to Dr. Fishman, we studied patients with moderate hypercapnia. I think it would be completely wrong to extrapolate from these observations conclusions regarding these very sick patients who have very high plasma carbon dioxide. In fact, I'm usually surprised when people report studies on patients with carbon dioxide tensions of 75 or 80 mm. of mercury in the arterial blood, because we found that those patients were too sick to do really satisfactory studies on.

THE VARIABILITY OF BEHAVIOR WITHIN THE EMPHYSEMATOUS LUNG[1,2]

W. A. BRISCOE

It is well known that the emphysematous lung is unevenly ventilated. It is not well known, however, how very unevenly ventilated it is. We will consider here the degree to which these lungs are unevenly ventilated, and we will supplement this by a consideration of the degree of uneven perfusion.

Nitrogen washout studies were followed by nitrogen washin studies in 10 patients with emphysema. During the nitrogen washout, the patients breathed oxygen for fifteen minutes. During the nitrogen washin, they breathed air for forty-five minutes. Arterial blood samples were obtained during the steady state while breathing air before and/or after these studies. The nitrogen washout studies agreed with the nitrogen washin studies in showing that a large part of the lung was very poorly ventilated. During the nitrogen washout, end tidal gas and mixed expired gas were alternately analyzed for nitrogen with a nitrogen meter. During the nitrogen washin period, mixed expired gas was analyzed for nitrogen with a Scholander apparatus. Analysis of washin and washout data agreed in showing that a large part of the lung was very poorly ventilated. On the average, 66 per cent of the lung received only 13 per cent of the alveolar ventilation. These alveoli in the slow phase of the lung were only one-twenty-third as well ventilated as the best-ventilated alveoli in the same lung. Well-ventilated in this context refers to alveolar ventilation per unit of lung volume.

The washout-washin method of studying the uneven ventilation of the lung has the advantage of giving a much more complete description of the uneven ventilation of the lung than do other methods. This is of value in quantitative consideration of blood-gas exchange. The measured lung volume and alveolar ventilation of the slow phase (the worst-ventilated group of alveoli), considered in conjunction with the lung volumes and ventilation of the better-ventilated groups of alveoli and the arterial oxygen saturation, give information concerning the distribution of blood flow to the lung. In most cases, it is found that the patient could not have an arterial oxygen saturation as high as the observed level unless the poorly ventilated alveoli were underperfused with blood. Underperfused in this context means that these alveoli receive less blood per liter of lung volume than do the well-ventilated alveoli, which means that there is less scatter in the ventilation-perfusion ratios in different parts of the lung than there is in the ventilation in different parts of the lung. On the average, the ventilation-perfusion ratio in the best-ventilated alveoli was ten times that in the worst-ventilated alveoli, whereas the ventilation per unit lung volume was twenty-three times that in the worst-ventilated alveoli.

General Discussion

Dr. Tenney: How is it that the lung does a reasonably good job over all despite the evidence of how badly the lung does *certain* of its functions? Given these deviations from the ideal ventilation-perfusion ratio distribution in the lung, what is the mechanism by which it functions reasonably well? Is it perhaps a reflex factor? We know that this can occur segmentally in the lung because, for instance, when a man lies on his side the dependent lung seems to have more blood, yet also increases its ventilation. Thus, although blood flow and blood volume are not always directly referable one to the other, under many circumstances they may be. Also, it is not clear that other animals, particularly animals that don't spend most of their lives standing upright with reference to gravitational field, make these adjustments as readily as does man. Therefore, there may be something unique in man. The statistical problem of trying to analyze this situation in quantitative form is a very formidable one, it seems to me.

People for years have known that there was such a thing as ventilation-perfusion ratio distribution in the lung. Haldane spent a great deal of time talking about it in his work on respiration. But the techniques for quantitative analysis are wanting. So far as models go, I think it can be shown mathematically that, so long as there is a symmetric statistical distribution of ventilation-perfusion ratios in the lung, an equivalent circuit can be made with two alveoli.

[1] From the Cardiopulmonary Laboratory Division, Columbia University, Bellevue Hospital, New York, New York.

[2] This investigation was supported by a research grant (H-2001 C) from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service.

On the other hand, the type of evidence Dr. Briscoe has presented (we too have been very much intrigued by washout patterns in the emphysematous lung—not using nitrogen but helium or sulfurhexafluoride) shows a washout curve which cannot be described by any two-chambered system. Indeed, it's not clear that it can be described by a three-chambered system. So the question is, what kind of a mathematical model can one construct for what must be a skewed distribution?

Another factor that I'd like to mention concerns the difficulty in finding satisfactory techniques for studying this problem. Ratios are always highly elusive because a change in a ratio can be either a numerator or a denominator change. For years people have known that the respiratory quotient is a function of the ventilation-perfusion ratio and that, in the normal lung and in caricature form in the emphysematous lung, there is, with the single breath expirate, a fractionation of the respiration quotient which would suggest that the alveoli which empty latest in the respiratory cycle have the lowest ventilation-perfusion ratio distribution.

I'd like to suggest that one of the problems that all of us face as respiratory physiologists is that we always talk about oxygen and carbon dioxide, but that there are other gases which could give some clues to some functions of the lung—perhaps to the ventilation-perfusion ratio distribution. This was pointed out by a person who refused to be prejudiced by his stuffy professors, namely, a second-year medical student, Bob Kenfield, who recognized immediately that there must be an abnormality in the nitrogen transport. But we never talk much about nitrogen transport. There is in the body a very reasonable and theoretically satisfactorily explicable nitrogen transfer. Alveoli which are relatively underventilated and normally perfused (in which, in other words, there is a low ventilation-perfusion ratio distribution) contain a high nitrogen pressure. This occurs because of the shape of the oxygen and carbon dioxide dissociation curves and the difference in the sum of partial pressures of all of the gas tensions in the arterial and venous blood, and because most alveoli are (in terms of their total pressure) in equilibrium with the surrounding barometric pressure and ambient air. This nitrogen pressure, again because of the distribution factor, will create an alveolar-arterial nitrogen gradient.

Second, there is another gas about which we're talking even less, and that is argon. Argon is present in low concentrations of about one per cent in the air. Because argon has a solubility roughly twice that of nitrogen, one would expect it to be picked up. Its diffusion coefficient is not much different from nitrogen, and one would expect it to be picked up in alveoli in direct proportion to their blood flow. Theoretically then, an analysis of the alveolar end-tidal argon-nitrogen ratio would give some index of what the ventilation-perfusion ratio through such alveoli would be. We tried this, and it's a very difficult thing to be satisfied with, but at least the trend is in the direction that might be anticipated.

My final comment is that we have neglected to explore in any detail one area of physiology which offers some promise to the understanding of disease, and that is comparative physiology. We have rather stereotyped concepts of what is normal for man. But there are lots of organisms existing in nature that get along quite well, yet we think of them as being quite abnormal with reference to our own standards. Dr. Fowler has already brought in the giant sloth as one such example. I'd like to just interject something even more dramatic, namely the flora domanitae, which has the lowest oxygen consumption per unit of surface area, I think, of any mammal; it also has the largest alveoli of any mammal.

With reference to ventilation-perfusion ratio distribution, there is something that's much more intriguing, and that is that birds exist with a ventilatory apparatus which includes almost two-thirds of the totally contained air space in the air-sac system, which is almost exclusively nonperfused. Because we've had some interest in ventilation-perfusion problems, for the last two years we've been studying gas exchange in birds, and it's quite extraordinary that there are many similarities between their pattern of gas exchange referable to the kind of analysis Dr. Briscoe has presented. It bears great similarity to pulmonary emphysema.

DR. LIEBOW: The physiologists have been dealing today primarily with means or even vector sums, and I think Dr. Briscoe's approach has reflected in part the complexity of the anatomic problem. As anatomists, we are required to make, so to speak, the unitary analysis of a lesion at a series of levels which approaches the infinite, which is a fair-sized job. Also, the physiologists have been dealing with late lesions in which obstruction is perfectly obvious, but this may in fact be the result of certain other factors in the pathogenesis of emphysema; for example, loss of tractional support of the bronchi. So the question which Dr. McLean has raised so thoughtfully, "What are the early lesions and what is their pathogenesis?" is still a very pertinent one because it would not only tell us, when solved, something about the nature of the disease, but maybe even something about how to prevent it.

EXPERIMENTAL STUDIES

WARD S. FOWLER, *Moderator*

PRESSURE-FLOW-VOLUME INTERRELATIONSHIPS IN MAN[1, 2]

ROBERT E. HYATT

Theoretical considerations of the pressure-flow-volume relationships of the lung (FRY, D. L.: Phys. Med. Biol. Lond., 1958, *3*, 174) suggested that the relationship of maximal expiratory flow to degree of lung inflation over the lower vital capacity was determined by the physical properties of the lung and intrathoracic airways. Since it is generally accepted that emphysema is a disease of the intrathoracic airways, it seemed important to study this relationship in normal and emphysematous subjects.

The relationship between the degree of lung inflation and the maximal expiratory flow that an individual can develop at that volume can be rather simply obtained. This relationship for the entire vital capacity (VC) range has been termed the flow-volume (F-V) curve. Over approximately the upper 50 per cent of the vital capacity the F-V curve depends on the subject's applying maximal force to the lung, this portion being called the β F-V curve. In contrast, over the lower half of the vital capacity, maximal expiratory flow in the great majority of subjects does *not* correspond to maximal effort, this region being termed the α F-V curve. The α F-V curve has been found (*1*) to be reproducible, (*2*) to be unaffected by wide variation in upper airway resistance, (*3*) to show on empirical analysis a wide separation between normal and emphysematous subjects, and (*4*) to show predictable changes when the physical properties of the respired gas were altered (helium-oxygen mixture).

Preliminary studies of smokers versus nonsmokers revealed a slight but statistically significant difference in the α F-V curves of the two groups, smokers tending towards the pattern seen in emphysema.

Our studies to date suggest that the α F-V curve may prove of value in the early, precise quantification of abnormalities in the mechanical behavior of the lung.

GENERAL DISCUSSION

DR. BEN V. BRANSCOMB (Birmingham, Alabama): In essence, Drs. Fry and Hyatt enabled us to get rid of the esophageal balloon.

Physiologists have devoted much effort to the problem of explaining what makes emphysema worse. For example, when a patient develops bullae or unequal filling of various parts of the lung or high intra-alveolar pressure that compresses capillaries, appropriate measurements will show that the disease is deteriorating. Uneven ventilation can lead to more uneven ventilation. Localized high pressures can perhaps produce ischemia or necrosis; poor bronchial toilette may result in infection. We have heard about the role of infection and inflammation—which incidentally are not the same—in the etiology of emphysema. We have heard very little about genetics, about the aging process of the lung, and almost nothing about the problem of bronchial spasm and bronchial obstruction on a muscular basis or bronchial obstruction caused by edema of the bronchial wall, with the exception of the edema that may be associated with inflammation due to infection

We have become very interested in a series of patients who we believe have early emphysema. Without going into details, I'll just say that all my patients have wheezing that can be heard at the end of a very forced expiration; they have wheezing that can be heard in all phases of their breathing, but they're never aware of it and have never complained of it. In fact, most of them have no complaints. Some of them have no evidence of infection or inflammation; some may have infection in the small bronchi, and thus be examples of the process that Dr. McLean showed us so well.

Nevertheless, one is tempted to speculate that these people have bronchial constriction of the kind that happens in asthma, a swelling or edema of the bronchial wall causing the type of obstruction that we saw with the rubber tubes here this morning. This prevents emptying of air and may thus lead to rupture of air spaces and progress into emphysema, which in turn becomes vulner-

[1] From the Cardiopulmonary Laboratory, National Heart Institute, Bethesda, Maryland.

[2] Entire article appeared in *Journal of Applied Physiology*, November, 1958.

able to infection. Perhaps more than one explanation is in order.

In trying to study these patients, we have gone through the same thinking that many of you have. We have put down esophageal balloons and measured pressure-flow-volume curves on these patients. We were trying to find whether they had small airway resistance, whether it varied from time to time, and what made it vary.

A logical experiment would be to try to find out whether normal bronchi are always in a state of varying diameters like peripheral blood vessels. Perhaps emphysema is a process that comes about like essential hypertension: the bronchi spend too much time in a state of constriction, resulting in a sequence that leads to breakdown of tissues.

Our one problem is that in our pressure-flow loops we are unable to compare the volume in two successive runs in the same patient. We also have the problem of analyzing a three-dimensional plot, pressure-volume-flow. Dr. Hyatt has demonstrated that we can eliminate one variable, namely pressure, by selecting certain specified pressures on our patients, the pressures at which maximal flows are available at a given volume. Then we can slice through our three-dimensional plot and simply examine flow and volume. This will aid those of us who are trying to study resistance in the small airways.

May I also say that most of the things Dr. Hyatt has pointed out are available to us on an ordinary spirogram. A spirogram, after all, is a measurement of volume and time, and from that one can get flow. The trouble is, you never know whether the bottom part of the spirogram really represents the patient's best effort. If the patient blows harder, the air may come out more slowly, as they have shown us. You may get closure of the bronchi and thus get less than maximal flow. The ideal spirogram would be one in which the patient applied just enough force to achieve a maximal flow at each volume as he passed through that volume. This information is not available to us clinically. It's hard to make such spirographic measurements, whereas with the technique that Dr. Hyatt has shown us it looks quite easy. All you need is a flowmeter, a differentiator, a spirometer, and an oscilloscope; in spite of the need for complicated instruments, it does look like a very valuable tool.

Dr. Hyatt says his measurements are not as volume-dependent as other methods are. This may not be strictly correct, it seems to me. Suppose the lung becomes inflated, say with blood, and therefore larger; this alters the compliance of the lung, alters the physics surrounding the terminal gas flow and, even though the spirometer might show that you are dealing with the same volume, it would not be so in this patient; hence on successive days, with or without treatment or other situations, comparable values might not be anticipated. Dr. Hyatt pointed this out. He said that you have to have the same mechanics in the terminal airways, the same compliance of the lung, the same diameter of the bronchi, the same gas to be breathed, and so forth, to get the same tracing. In addition, this technique is not a measurement of bronchospasm. It measures a complex relationship between a number of factors of which spasm, edema, and compliance are just some contributing elements. Nevertheless, I think this technique may open the way toward comparative studies in patient groups, by which we may learn more about early obstruction in emphysema. The study of early patients will be necessary before we learn very much about its etiology.

Dr. Hyatt: If a subject starts at the maximal inspiratory point and does a "choo-choo" train type of breathing right on down to the end of the vital capacity, we get a maximal expiratory flow-volume curve; it is different from the usual curve presumably because the compliance and various other properties of the lung are different with this sort of rapid cyclic-type of breathing, in comparison with one where you take a deep breath and go through your whole vital capacity in one breath. This is presumptive evidence that the physical properties of the lung can change, depending on how you measure it.

Dr. A. North Longfield (Albuquerque, New Mexico): We have been very interested in our spirograms and have approached the problem by curve fitting. We found that in most of our spirograms we could express the expiratory curve by the formula: volume is equal to a constant times the log of time. This is a formula which is derived empirically, and there are small variations from the theoretic curve. We found that, if time is expressed in terms of millimeters, and since our spirogram is taken at a speed of 32 mm. per second, it is possible to separate emphysema patients from normal subjects. The normal subjects have a constant of more than one, and the emphysema patients have a constant of less than one.

In a spirogram of a cough, the lower portion could be expressed by a similar formula; the upper portion of the cough spirogram, however, exceeded the flow that we were able to obtain in a fast expiration. We found that the volume of this first fast component of cough was critical in respect to differentiating normal subjects from emphysema patients.

For those of you who believe that spirograms are fallible, we believe the same thing, except for the fact that we are able to demonstrate this same phenomenon with the pneumotachograph. We think that this particular demonstration is important in that we are able to express the whole

curve both in fast expiration and in cough by a formula. The fast portion of the curve in cough exceeds the maximum that people are able to get out in a fast expiration. This exacts a penalty, due to the trapping effect, so that the lower portion of the curve in cough is a good deal slower than in a fast expiration.

DR. DAYMAN: It has been our experience that expiration by a series of coughs duplicates the pattern of flow for an expiration of maximal flow and volume. That is to say, if we remove from consideration the part of the pneumotachograph tracing where flow is zero due to complete glottic closure, the remainder comprises a maximal expiratory flow pattern except for the initial peaks which have special significance. As the glottis opens, the intrathoracic airways are subjected to compression concurrently with the establishment of flow. They narrow until adjustment to the dynamic conditions of flow are achieved. The narrowing extrudes air and this is expressed in the pneumotachograph as an initial period of augmented flow lasting less than 0.1 second. The peak of flow terminates abruptly at a point where a slower rate of deceleration becomes established by the narrowed airways. The juncture of these segments forms an angle which we call point of closure.

Another change occurs when approaching the expiratory terminus of the breath. Deceleration at this point becomes even slower, and the change usually takes place when the rate of expiratory flow is approximately 0.5 liters per second. We believe that this is the point where lung tension has become zero. We know the volume exhaled to this point and we can assume in health that there is a change of lung tension from 25 cm. of pressure to zero. From this we can compute the compliance of the lung. This appears to hold true for healthy subjects and for those with interstitial pneumonitis, as Dr. John Sharp showed us by measuring the compliance in a case of this disease. Unfortunately it does not appear to hold for the obstructive conditions. (Observations made since the conference indicate that, in obstructive states due to intrinsic disease of the airway system, there is another variable—bronchiolar compliance—which modifies the relationship between critical expiratory flow and lung tension.)

These are examples which suggest that detailed analysis of flow can yield precise and useful information. In the past five years, wherever this type of analysis could be applied, we have done so in medico-legal cases and the logic of the interpretations has usually seemed convincing to those responsible for adjudicating the case.

CHRONIC ALVEOLAR EMPHYSEMA IN THE HORSE[1]

A. F. ALEXANDER

Chronic alveolar emphysema or "heaves," a specific syndrome in horses, is characterized by expiratory dyspnea, cough, and lack of endurance to exercise. The condition is slow in development, prolonged in course, and irreversible in nature.

The disease usually affects animals more than eight years of age and involves males, females, and neuters in equal proportions. Prior to the mechanization of farm and trucking power, emphysema was a serious and common disease among horses. The incidence of this disease has decreased markedly during the past two decades due to the diminished population of draft and stabled horses, and the condition is now only occasionally encountered.

The specific etiology is unknown. The condition has most often been associated with horses that are stabled and are fed dusty or mouldy hays. Timothy, alfalfa, and clover are usually incriminated. In the latter part of the nineteenth century the disease was reported to be virtually unknown in those portions of the world where winter feeding of hay and stabling were not practiced or in those areas where the above hays were not fed. The disease was said to follow cultivation of the land and the stabling of horses. It is only rarely encountered in those animals which are continuously pastured or fed native grass hays.

Chronic bronchitis induced by fungus and rusts developing on the hay, either before or after cutting, has been thought to play a prominent etiologic role. It was noted that the disease was frequently encountered when hays from climates with heavy rainfall were fed. A postulation was made that the climatic conditions were conducive to rust infections of the plants and to molding of the hay after cutting. Observations were also made that emphysema less commonly developed when irrigated hays from arid climates were fed.

Prolonged exhaustive work, or short intensive work, especially with a distended digestive tract, has also been incriminated in the etiology of this condition. However, since the disease is slow in developing, it may be that at the time of exhaustive or intensive work the marked signs are first noted. Heredity has not been shown to be a significant factor in the development of this condition.

Primary pulmonary disease, such as chronic bronchitis and pneumonia, is often thought to be a precursor of chronic pulmonary emphysema. Conditions leading to a chronic persistent cough are often involved. Most likely a combination of the above suspected etiologic and predisposing conditions are responsible for development of the malady.

The exact pathogenesis of the disease is also unknown. It is most widely held that a chronic bronchitis with persistent coughing is antecedent to the condition. High intra-alveolar pressures from coughing and forceful respiratory movements with partial bronchiolar occlusion are thought to cause distention and/or rupture of the alveoli, followed by mild septal fibroplasia, loss of elasticity, and diminished magnitude of capillaries. The restricted vascular bed and associated resistance to circulation are thought to account for the frequently observed right ventricular hypertrophy which may develop into a congestive right heart failure.

The most prominent signs of the disease are expiratory dyspnea, a dry nonproductive cough, and reduced endurance to exercise. In well-developed cases the dyspnea is characterized by a double expiratory movement with development of the so called "heave line" along the costal arch. First a normal passive expiration occurs followed by an active one in which the abdominal musculature contracts. It is this contraction, with probable resultant muscular hypertrophy, which forms the so called "heave line." At rest the animal's nostrils remain dilated. All of these signs are markedly accentuated following exercise, during which the animal is very easily fatigued.

Serous nasal discharge and intestinal flatulence are also frequently associated with this disease. In advanced cases the thorax may appear permanently distended. Severely affected animals lose weight and become unthrifty despite rav-

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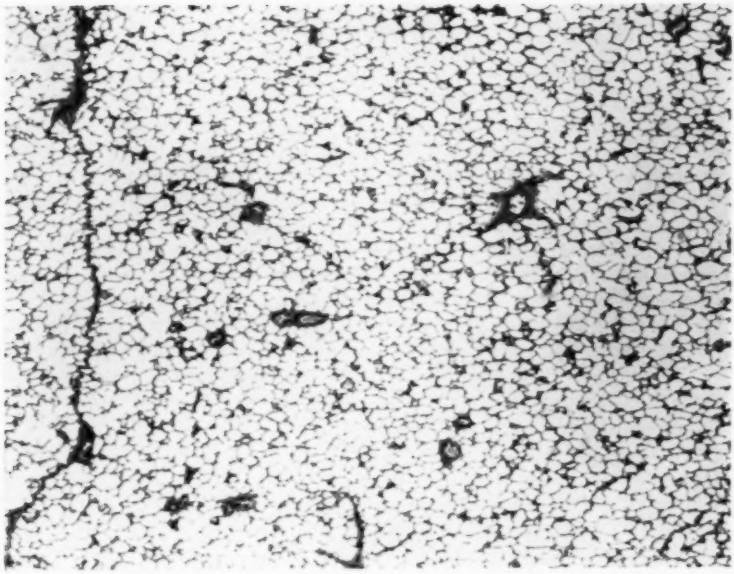

FIG. 90. Normal equine lung. (Hematoxylin and eosin stain, × 18).

enous appetites. The signs may also be aggravated by exposure to inclement weather, high humidity, dusty, mouldy, or bulky forage, chilling, and mild respiratory infections.

The course of the disease is protracted, usually progressive, and extends over months or years. It is irreversible in nature and, although the animal may be used for light work, it eventually becomes worthless. In advanced cases, signs of congestive right heart failure may be noted with development of edematous swelling along the ventral thoracic and abdominal walls.

Upon opening the thoracic cavity at necropsy, the lungs in well-developed cases tend to remain distended. They are pale in color, have rounded edges, and pit on pressure. Rib impressions may be seen, and emphysematous bullae may be present. The changes are usually most prominent at the dependent and posterior borders of the lungs. Lesions of bronchitis may be seen throughout the lung. In advanced cases right ventricular hypertrophy and lesions of congestive heart failure may be noted.

Microscopic examination of involved areas reveals distended and ruptured alveoli with thin alveolar walls. In these portions stretched capillaries show reduced luminal diameters and may be empty. Fibrosis is often seen in septal structures and in the peribronchial areas. The most constant finding is that of chronic bronchitis and bronchiolitis (figures 90, 91, 92).

Therapeutic measures are mainly palliative in nature. Limiting the amount and severity of work, feeding less bulky and dust-free hays, placing the animal on pasture, and protection from inclement weather will help to reduce severity of the condition. Administration of atropine will afford transient relief, probably through its bronchiolar dilating action. The fundamental changes are, however, irreversible and the condition usually becomes progressive.

The significance of this disease is that it is now only occasionally seen and is of relatively minor importance in clinical veterinary medicine.

General Discussion

DR. ROBERT F. GROVER (Denver, Colorado): Do you know if this clinical and pathologic picture which you have presented occurs spontaneously only in the horse?

DR. ALEXANDER: There have been reports in the old literature—and I mean back at the end of the nineteenth century—that this occurred in hunting dogs. However, to my knowledge and as far as I can determine, this is not the case, and I

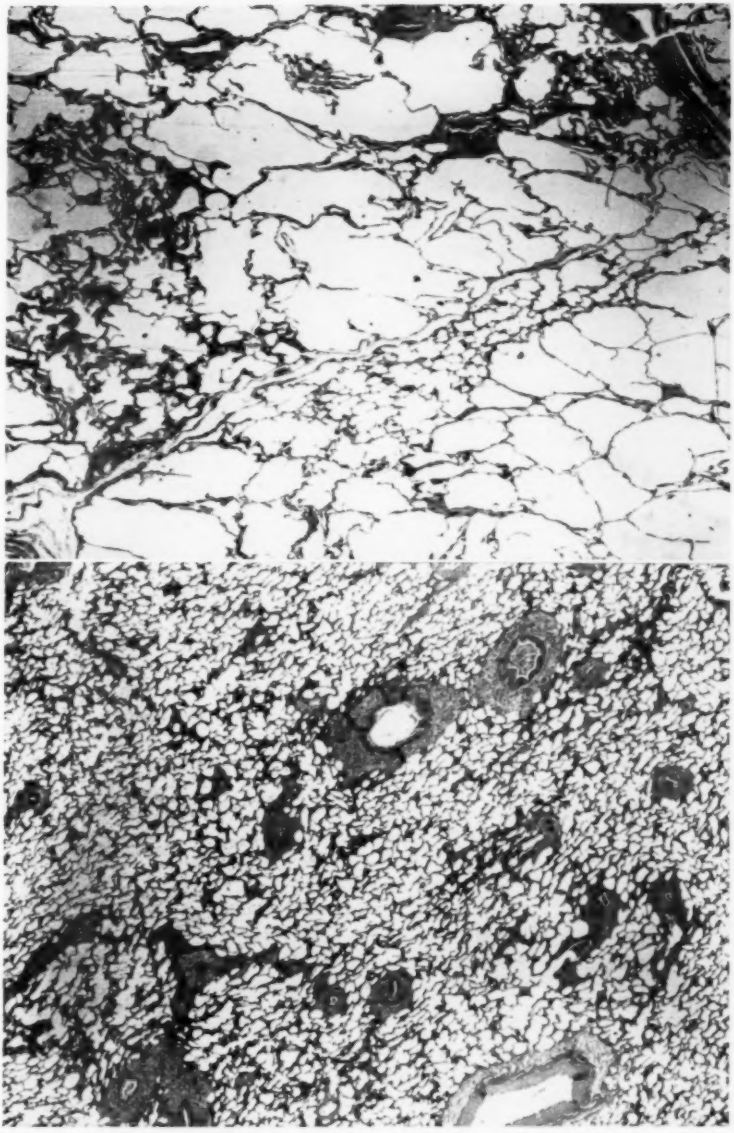

FIG. 91 (Top). Lung from horse with clinical signs of emphysema showing distended and ruptured alveolar septa. (Hematoxylin and eosin stain, × 18).

FIG. 92 (Bottom). Same as figure 91, showing bronchiolitis and peribronchial infiltration. (Hematoxylin and eosin stain, × 18).

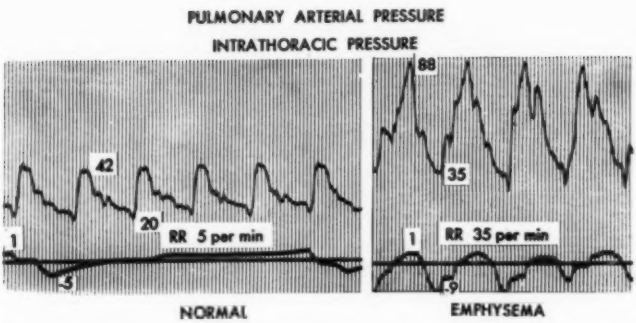

FIG. 93. Pulmonary arterial pressures and respiratory rates (RR) in a "normal" versus an emphysematous horse.

believe that this condition, as we presented it here, is only in the horse. There is acute pulmonary emphysema in cattle, but this is something entirely different and unrelated to what we're covering here.

DR. GROVER: I am sure that we would all agree that the picture of emphysema in the horse which Dr. Alexander has presented bears many striking similarities to the disease entity or entities which we are considering in this conference. Certainly the implication of dust as an etiologic agent in heaves in the horse, the requirement for a long-standing persistent cough, respiratory infection, bronchitis, bronchiolitis; these are all reminiscent of the history in human cases. I am sure that his beautiful photomicrographs were extremely suggestive of the ones which Dr. McLean showed and the widespread presence of bronchiolitis was most impressive.

I had the privilege and opportunity of working with Dr. Alexander in making certain physiologic observations on this animal and on a normal animal. To my knowledge, these are rather unique observations. The emphysematous horse and the normal horse were subjected to cardiac catheterization, which proved to be a surprisingly simple procedure. The animals were awake and standing. They had been tranquilized and were most cooperative. We used a standard human cardiac catheter, passed it with pressure monitoring, and it went directly to the pulmonary artery. A number of things are quite obvious in figure 93. The pulmonary arterial pressure in the normal horse is certainly higher than is seen in normal man, but there is a marked paucity of normal values for the horse in measurements of this type. There is no question that the emphysematous horse had pulmonary hypertension, when compared with the normal animal here. There is a very obvious marked difference in the respiratory rate, 5 as against 35 in the emphysematous animal. The double hump in expiration, the "heave" in the emphysematous animal, is apparent here. It may also be noted that the swings in intrapleural pressure were somewhat greater in the emphysematous animal, and these presumably reflect intrathoracic pressure. In the normal animal there is very little respiratory variation in the pulmonary arterial pressure, whereas the bulk of the oscillation in the pulmonary arterial tracing in the emphysematous horse is due to the respiratory waves.

We found that the normal animal had an arterial saturation of about 89 per cent. Again normals are lacking. This would seem a bit low, but the emphysematous animal definitely had arterial unsaturation, viz., 79 per cent. The carbon dioxide content of the arterial blood, 51 volumes per cent, again by human standards, would be elevated. However, this value is not significantly different from that in the normal animal. Either both or neither of these animals had carbon dioxide retention, we can't say which. We did measure the carbon monoxide diffusion capacity in the emphysematous animal. It was 38.2, but we have nothing to compare it with. Therefore, I simply say that it is possible to measure it.

In summary, we all realize that we are dealing with a disease process about which we do not know a great deal, and I refer to the disease in man as well as in the horse. Whenever we are faced with a problem such as this in medicine, it has been proved repeatedly that the availability of an experimental animal with which we can work is a great asset in advancing our knowledge of this disease process. It appears that we have here a disease very similar, in many aspects, to human emphysema. It occurs spontaneously in the horse, and potentially this observation could be of con-

siderable value in elucidating emphysema as we are trying to understand it.

DR. FOWLER: I've been told that Shetland ponies may also develop heaves.

DR. FRANCIS C. LOWELL (Boston, Massachusetts): I'd like to ask Dr. Alexander whether, in using the word "irreversible" in this condition, the ultimate test in irreversibility has been applied to this disease. In other words, have any of these animals been treated with full doses of steroids? In the figures, what looks like an inflammatory lesion surrounds the bronchioles, as you have described. It is quite conceivable that a good deal of this would subside under intensive steroid therapy, as apparently similar lesions seem to do in bronchial asthma in man.

I also take issue with Dr. Dayman on the question of the use of epinephrine or any other bronchodilator substance in trying to decide whether a patient is treatable or not. I think the only way to find out whether a patient is treatable is to give him the ultimate in such treatment, namely, full dosage of steroids.

DR. BRANSCOMB: One thing that struck me about this horse was that the evidence for structural lung damage was really slight in the light of the remarkably high pulmonary arterial pressure.

DR. ALEXANDER: I have no explanation for the apparent disproportion between the extent of the pulmonary disorder and the cardiac problem in this animal.

DR. HECHT: As time goes on we should pay more attention to comparative pulmonary physiology. The horse has a very high cardiac output; oddly enough, the output in animals of this sort does not go along with the index. In consequence, an elevation of pulmonary arterial pressure has to be interpreted in line with the output. That is, the resting output may not be unusually high with this degree of flow, though I agree that in the emphysematous horse presumably there are pulmonary vascular changes which caused the findings you have reported. Furthermore, these animals, far from being placid and easily handled, are rather excitable. Under what circumstances were these pressure tracings obtained?

DR. GROVER: This animal was studied under the influence of Thorazine®; he was most cooperative, I assure you. He had a heart rate of 40 per minute, which is some indication of his state of relaxation. The cardiac output of this animal was 21 liters per minute; and, using the formula of Brady, Comfort, and Matthews for surface area in animals, his cardiac index was 3.7 liters per minute. It's somewhat in keeping with the low output we see in human emphysema. I don't pretend this is a natural state; unfortunately, it was measured under anesthesia.

Furthermore, the animal's arterial saturation was considerably lower under chloral hydrate anesthesia than when he was awake. I agree, this is a low output. If you use the index and the pressure to calculate the pulmonary resistance, it comes out 1,200 dynes-second-cm^{-5}-m^2, and that's definitely high. If you don't correct for body surface, it's 200. We believed that this animal had evidence of increased pulmonary vascular resistance as well as a low output.

DR. FOWLER: The pulmonary arterial pressure has been measured in a giraffe. The giraffe has a thorax four to five feet long. It would therefore be necessary for the giraffe not only to have terrific systemic hypertension but to have pulmonary hypertension as well.

DR. FISHMAN: The dog is said to have higher pulmonary arterial pressure than is found in man, in the order of 35 systolic; at least these are the old data of Hamilton.

DR. HECHT: By hearsay the pulmonary arterial pressure in the giraffe is not particularly high.

DR. FISHMAN: Unless someone can really document anatomically the position of the atrium, it might be that these few millimeters' difference in the horse may not really mean too much. Will Dr. Alexander please discuss the question of emphysema and Brisket disease in cattle?

DR. ALEXANDER: I prefer the term "high mountain disease of cattle"—it is a syndrome which exists in cattle which range at elevations over approximately 7,000 feet. The incidence is roughly estimated at between 0.5 and 1.0 per cent of animals over that elevation. It is a syndrome of right heart failure and the signs and the lesions of this disease can be interpreted in that light. Emphysema is not a major part of this condition, although there is debate on this. It may be due to multiple pulmonary infarcts or emboli.

DR. ALBERT ROBERTS (Washington, D.C.): Regarding the statement that emphysema is irreversible, I know of a case in point. Some old horses condemned for being emphysematous were taken up by a few kind ladies outside of Boston. Later they called in a physiologist to see how the horses were doing. He found no evidence of emphysema in the horses. The only explanation he could give was that these ladies were feeding their horses cooked meals. Hence, there's a question whether that particular emphysema was due to some hypersensitivity phenomena.

DR. THEODORE GLEICHMAN (Denver, Colorado): The ranchers in Colorado say that there is no mystery about the heaves. They almost universally seem to feel that it's due to feeding on

mouldy or dusty hay and to overwork. This brings to mind the elephant, which is characteristically fed hay off the ground. Has anyone ever seen this syndrome in elephants or autopsied elephants to find out about it?

DR. FOWLER: I helped autopsy one, but that was before I ever heard about emphysema.

DR. BRANTIGAN: Could I ask Dr. Alexander if he has any information about the use of tracheostomy in the heavey horse?

DR. ALEXANDER: No. This disease is very rarely seen today, and those animals that do develop it nowadays are not nearly as sick as they used to be.

DR. FOWLER: Have heavey horses been treated with steroids to your knowledge?

DR. ALEXANDER: No, not to my knowledge.

EXPERIMENTAL EMPHYSEMA[1]

B. EISEMAN, T. PETTY, AND W. SILEN

INTRODUCTION

A precise and objective study of any disease usually awaits its successful production in an experimental animal. This fundamental thesis is glaringly evident in the study of emphysema, in which reports are often grossly biased by the enthusiasm or bitterness of the clinical observer. It seems of prime importance, therefore, to devise a reliable technique for the production of this syndrome in experimental animals, in which the disease and its treatment may be studied with a high degree of objectivity.

This is a critical analysis of methods previously employed to produce experimental chronic obstructive (hypertrophic) emphysema in animals.

Brown-Sequard (1) first attempted to produce experimental emphysema in 1871 by stimulating the vagus nerve or its central nuclei in dogs and rabbits, and claimed thus to have produced the disease by causing acute bronchial spasm. These experiments lasted but a few days, and no objective evidence of results was presented.

TRACHEAL OBSTRUCTION AND OVERINFLATION AS A MEANS OF PRODUCING EMPHYSEMA

In 1877, Kohler (2) partially ligated the trachea in rabbits and after several weeks noted alveolar dilatation but made no claim that he had produced emphysema. Other investigators (3–7) have used various methods for partially obstructing the airways of animals and thus overinflating the lungs, but none has resulted in unequivocal emphysema. Chillingworth (8) placed animals in a low-pressure chamber with the lungs exposed to the greater atmospheric pressure via an endotracheal tube leading from the low-pressure box. Rasmussen and Adams (9) used biweekly positive pressure insufflation for as long as eleven months, but in neither of these studies was there evidence of more than an overinflation of the lung with occasional alveolar rupture.

A variety of endotracheal valves have been devised in an effort to produce chronic expiratory obstruction in experimental animals. Harris and Chillingworth (10) used a ball valve in 25 dogs for periods ranging from one day to three weeks, but the distended lungs that resulted differed little from those of the control animals in which no ball was placed in the tracheal tube. Such devices have been used by others for periods ranging from a few hours (11) to eight months (12–14). Although characteristically resulting in overdistention of the lungs with rupture of alveoli, none of these experiments has produced even the morphologic picture of chronic obstructive emphysema.

Paine (15) utilized an endotracheal hinge valve in a similar manner and believed that the resulting pulmonary morphologic changes resembled emphysema. Of more importance, he, for the first time, utilized pulmonary function tests (pulmonary distensibility) as an objective parameter for evaluating his experimental method. His data demonstrate that intrapleural pressures were decreased following insertion of the valve but do not conclusively show an alteration in lung compliance.

Currently the present investigators (16) are studying a group of dogs in which a small tube (figure 95) has been inserted into the trachea that produces 50 to 60 per cent more turbulence (and therefore resistance) on expiration than in the relatively unhindered inspiration (figure 94). We have also performed preliminary studies in attempting to produce expiratory bronchial collapse (and thereby obstruction) by fracturing or excision of bronchial cartilages.

Experimental approaches of this kind were at first designed to produce acute pulmonary overdistention which was confused with emphysema. More sophisticated experimental rationale maintains that prolonged pulmonary overdistention will produce thinning of the alveolar walls, subsequent narrowing of alveolar capillaries, and finally, fragmentation of the fatigued and relatively avascular alveolar elastic fibers. Such results would indeed simulate the morphologic changes of obstructive emphysema. There are at least two limitations to this experimental approach. The first is that adjacent portions of the lung may have to be differentially obstructed so

[1] From the Department of Surgery, University of Colorado School of Medicine; and the Denver Veterans Administration Hospital.

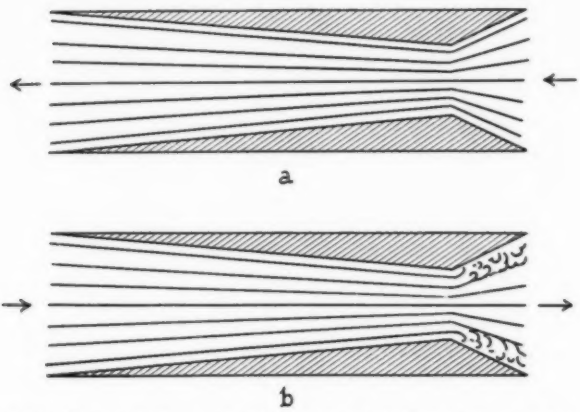

FIG. 94*a*. Air flow starting at shallow end unimpeded. *b*. Air flow starting at the deep end impeded by turbulence at the shallow end.

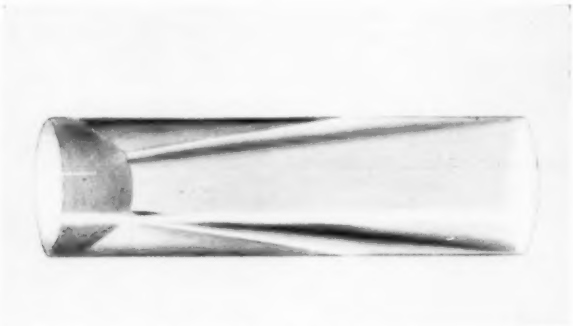

FIG. 95. Plastic tube for the production of experimental emphysema causing extreme turbulence on expiration but no resistance to inspiration.

that air may be trapped in one area where the alveoli suffer inordinate expiratory stress, while adjacent tissue remains relatively collapsed and resilient, a situation that is known to occur clinically (17). Experimentally this would require placement of the obstructing device in a bronchus rather than in the trachea. The second, and perhaps more valid, criticism of such techniques is that available evidence suggests that normal alveoli will not rupture at physiologic pressures (18, 19).

ALTERATION IN SIZE OR SHAPE OF THE RIB CAGE

Freund (20) first suggested that pulmonary emphysema was primarily an abnormality of the thoracic cage.

In 1927, Nissen (3) attempted to produce emphysema by enlarging the size of the thoracic cage by interposing a metal bar between the ribs and the sternum of dogs. The experiments lasted but twenty-four hours and did not produce emphysematous changes. Although the cardiopulmonary manifestations of severe kyphoscoliosis may resemble obstructive emphysema, the primary pathology of the two diseases is fundamentally different, for in kyphoscoliosis the lesion is one of decreased elasticity and excursion of the thoracic cage (21) and not of the pulmonary parenchyma.

It would seem that experiments designed to alter the size, shape, or elasticity of the rib cage might produce overdistention or perhaps the cardiovascular lesions that occasionally accompany severe emphysema, but offer little promise

of experimentally duplicating chronic obstructive emphysema.

REEFING OF THE DIAPHRAGM

By reefing and thus lowering the diaphragm in 7 dogs, Paine (15) increased the volume of the thoracic cavity and claimed to have produced emphysema as evidenced by morphologic changes and a decrease in pulmonary distensibility. Restudy of his data suggests that there is little significant change in lung compliance.

COMPENSATORY OVERDISTENTION

The compensatory pulmonary overdistention surrounding an area of atelectasis or adjacent to an excised segment of lung has suggested this experimental approach to the problem. Nissen (3) produced such adjacent pulmonary overdistention in 1927 following ligation of either bronchial or pulmonary arterial segments. Although frequently (22–24) compared to hypertrophic emphysema, such simple overdistention has clearly been shown by McIlroy and Bates (25) to differ from chronic obstructive emphysema in the following details.

	Lung Volume	Intrathoracic Pressure	Gaseous Diffusion Capacity
Overdistention	Increased	Decreased	Normal
Emphysema (hypertrophic or chronic obstructive)	Increased	Normal	Decreased

It would seem that efforts to produce simple pulmonary overdistention will contribute little to our knowledge of true obstructive emphysema.

CHRONIC HYPOXIA

In an effort to produce emphysema by hyperpnea, Campbell (26) exposed small animals to low oxygen concentrations, but the morphologic changes that he believed were due to emphysema merely represented patchy areas of overdistention adjacent to congested and hemorrhagic portions of the lung.

Prinzmetal (27) similarly claimed to have produced experimental emphysema in rats by keeping the animals chronically hypoxic. He reasoned that hypoxia and hypercapnea lowered intrapleural pressure, which in turn would cause overdistention of the lungs and subsequent emphysema. His only experimental evidence for producing the disease were some photomicrographs showing overdistended alveoli. Similar morphologic changes were noted in rats maintained at atmospheric pressure of 350 mm. of mercury for one to ten weeks, and the suggestion was made that living at high altitude predisposes to emphysema.

BRONCHOSPASM, ASTHMA, AND COUGH AS A MEANS OF PRODUCING EMPHYSEMA

Because of the clinical relationship between emphysema, on the one hand, and bronchospasm, asthma, and chronic bronchitis, on the other, the experimental production of these diseases has been used in an effort to produce obstructive emphysema.

Auer observed that the lungs of animals dying from anaphylactic shock remained distended, and suggested that emphysema might be produced by a more chronic form of such bronchospasm (28). Cloetta studied this response more specifically in the cat lung suspended in a vacuum and showed that, if histamine were administered immediately prior to death, the lung remained distended compared to the collapsible nontreated control animals (29). Hoover in 1922 showed that such pulmonary distention secondary to bronchospasm was not true emphysema and emphasized that it was necessary to provide an uneven distribution of expiratory stress throughout adjacent areas of the lung to produce emphysema (30).

Prinzmetal studied the effect of such bronchospastic drugs as eserine and pilocarpine in trying to produce emphysema (27). He was able to increase the chest girth of the dogs, to decrease intrapleural pressure, and to produce ruptured alveoli, but not to produce chronic obstructive emphysema.

Creation of a chronic cough in the experimental animal might be investigated as a means of producing obstructive emphysema. This could be done by a small subcutaneous secondary coil that is intermittently activated by a primary coil wound around the animal cage—a method that previously has been used for other experiments involving chronic nerve stimulation (31).

ALTERATION OF PULMONARY VASCULATURE AS A MEANS OF PRODUCING EMPHYSEMA

The obliterative pulmonary vasculature changes characteristic of emphysema have been considered by some to contribute to elastic tissue degeneration and loss of alveolar substance (32,

33). This approach to the experimental production of emphysema is currently being investigated by Canada (34).

DESTRUCTION OF PULMONARY ELASTIC TISSUE

Prominence of pulmonary elastic tissue degeneration in emphysema suggests that measures such as chronic bacterial infection (chronic bronchitis); experimental lathyrism (35); or enzymes of specific elastic tissue degenerative capacity might be of either primary or adjunctive value in producing experimental emphysema.

Crowle in our laboratory (36) has thus produced degenerative pulmonary changes morphologically resembling emphysema by ingeniously sensitizing experimental animals to their own pulmonary tissue.

PARAMETERS FOR JUDGING PRODUCTION OF EXPERIMENTAL EMPHYSEMA

Previous investigators have almost without exception been content to judge achievement in producing emphysema by mere observation of distended or ruptured alveoli. In many photomicrographs allegedly showing emphysema in the experimental animal, no attention has been directed toward such obvious microscopic criteria as the thickness or vascularity of the alveolar septa or to the state of the elastic tissue. Future efforts in this field must be judged by more exacting objective standards. In our own experience, dogs have been observed after months of expiratory obstruction with distended and ruptured alveoli and even with the occasional subpleural bleb when objective standards such as chest girth, functional residual capacity, and lung compliance have been unchanged.

In order to differentiate between simple pulmonary overdistention and actual chronic obstructive (hypertrophic) emphysema, the following objective and quantitative parameters are suggested for evaluation of experimental preparations.

1. Lung biopsies taken before and serially after producing the disease. Microscopic examination should include elastic tissue studies and interpretation not only of alveolar rupture but also of the finer and more precise changes characteristic of emphysema.

2. Gross description and determination of specific gravity of the lungs with measurement and photograph of blebs.

3. The following pulmonary function tests, all of which can be performed on the dog (10), should be performed two or three times in the control period and repeated thereafter: (*a*) functional residual capacity; (*b*) lung compliance; (*c*) carbon monoxide or other gaseous diffusion capacity.

It is further suggested that future investigators should consider the length of the experiment as it relates to the life span of the species under study. An acute experiment is unlikely to produce the disease in any animal, so that a study over a significant segment of the life span of an experimental animal may be necessary. Clinical emphysema usually does not develop acutely, and it is likely that neither will it do so in the experimental animal.

SUMMARY

A critical summary has been presented of previous attempts to produce experimental emphysema in animals. It is concluded that none has as yet proved successful. Current approaches to the problem have been discussed and parameters for judging future attempts have been suggested.

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GENERAL DISCUSSION

DR. FOWLER: I know of a lady who had a severe laryngeal obstruction for several months, enough to bring her maximal breathing capacity down into the 20's. After an operation to reopen the glottis, her lungs functioned quite normally.

DR. DAYMAN: Obstruction above the inlet of the thorax impedes the inflow of air rather than the outflow, with the result that the effects are exactly the opposite of those in emphysema. The lungs become smaller. A medical student with laryngeal stenosis has provided us with an excellent example of the change.

DR. EISEMAN: They get over it if they haven't had infection for too long a period, in my short experience. Is that the experience of others?

DR. BATES: There was an interesting patient described in the British Heart Journal (1958, *20*, 147). This case report dealt with an 18-year-old boy who complained of dyspnea on exertion which had caused him to forego any strenuous activity. He had a normal chest roentgenogram and was shown to have a tracheal vascular ring causing dyspnea which had been successfully relieved surgically. This ring had obviously been present all his life, but according to the case report, after cor-

rection of the long-standing tracheal stenosis he was left without dyspnea and, I assume, without emphysema.

Second, I would like to direct Dr. Eiseman's attention to the technique used by Professor Duguid in Newcastle (J. Physiol., 1953, *121*, 8) whereby he reports that he can measure the internal surface area of the lung. This is getting much closer to what ought to be measured and, as his technique should be easy to apply to animals, I think it would be well worth the attention of people who want to prove that they have altered the internal surface area of alveolar tissue in relation to gas volume.

Dr. Gaensler: I am treating a 40-year-old woman who had had a lobar obstruction for a long time. At operation this lobe would not collapse and it was pale; following removal it proved to have a pathologic picture exactly like chronic obstructive emphysema. In other words, an obstruction, which was certainly present for forty years or more, can apparently produce localized, typical emphysema.

Dr. Middlebrook: We have developed an apparatus to induce air-borne infection in animals. We can control the size of the droplet nuclei by incorporating, for example, various amounts of glucose, sucrose, or glycerol in the fluid. We can also control the depth to which various particles will go into the respiratory tract. Physiologists may find some use for this apparatus in studying human lungs.

Dr. Loosli: We have produced lung collapse in the dog by corroding the main-stem bronchus with 35 per cent silver nitrate. Without superimposed infection the bronchus will obliterate completely and the lung will collapse in about six weeks. If infection occurs behind the constriction, it will cause a chronic bronchitis which might be useful in some of your long-term experiments.

Dr. Fishman: Professor Gough shows a patient who had had asthma for twenty-five years at the time of autopsy and who had none of these destructive alveolar phenomena that we identify with chronic obstructive emphysema. It is well documented that it is impossible to produce experimentally anything that looks like chronic obstructive emphysema simply by putting an obstruction in the main airway.

Dr. Stead: In order to produce emphysema experimentally, it would be necessary to introduce mild chronic irritation fairly far down in the bronchial tree, perhaps with cigarette smoke or nitrogen dioxide in small doses, for instance.

AN ATTEMPT TO PRODUCE EMPHYSEMA IN THE GUINEA PIG[1]

ALFRED J. CROWLE

Some of the experimental methods for inducing emphysema-like disease in lower animals have just been reviewed for you. I should like to discuss very briefly the rationale behind one of these which assumes that emphysema can result from autoimmunologic reactions in which animal victims destroy certain constituents of their own lungs, so that these organs fail to function normally. My discussion will include some results from two pilot experiments set up according to this rationale.

Until recently a rule of immunology dictated that, since to react immunologically to their own tissues and to destroy them would contradict the concept of evolution, such reaction was unthinkable. However, considerable data leave no doubt now that immunologic and supposedly defensive mechanisms can backfire and injure the animal they were meant to protect. A malfunction of the thyroid gland in human beings, known as Hashimoto's disease, very likely is due to the production by the victim of circulating antibodies against his own thyroglobulin, a protein peculiar to that gland. This autoimmunization occurs only in rare individuals, and for yet little understood reasons.

A disease similar by cause is encephalomyelitis in which the victim has been vaccinated against rabies virus, for example, the virus suspension injected being contaminated with nerve tissue in which it was grown. In this disease, reaction against a foreign tissue apparently is followed by a cross-reaction of the victim with his own tissue. Encephalomyelitis can be induced at will in guinea pigs by injecting them with guinea pig brain homogenate emulsified in Freund's adjuvant.

The active ingredient of this adjuvant, killed mycobacteria, can intensify antibody formation, induce animals to form antibodies against their own tissues, and provoke delayed hypersensitivity to the antigen injected along with it. Some weeks after their injection with Freund's adjuvant and brain homogenate, guinea pigs develop limb paralysis due to histologically evident encephalomyelitis. The multiple activity of Freund's adjuvant requires that extensive investigation of any artificially induced autoimmunization disease precede explanation of its mechanism.

Emphysema could be due to autoimmunization. Slightly injured lung tissue, due, for example, to inhalation of chemically reactive fumes or large volumes of tobacco smoke, could make it foreign antigenically to the victims' immunologic processes. Many microorganisms can function as adjuvants: molds, spores, and bacteria associated with chronic lung diseases are good examples. Thus, with this small amount of injured tissue in proximity with an adjuvant, the victim is primed for autoimmunization. If the affected lung tissue happened to be elastic tissue, for example, emphysema might be its most obvious manifestation.

This hypothesis seems to be supported by our two pilot experiments using guinea pigs.

Three of these animals were injected subcutaneously with Freund's adjuvant, containing guinea pig lung homogenate. This homogenate was prepared from a guinea pig killed slowly by nitrogen oxide gas meant to injure its lung and to change slightly the chemical constitution of lung protein. Other than the single subcutaneous injection, the 3 injected guinea pigs received no other treatment which might have affected their lungs. Approximately three weeks after their treatment, all 3 began breathing abnormally, their diaphragmatic movements being exaggerated. After five weeks, 2 of the three animals died. The third was killed at the same time for comparison.

Major organs, except the lungs, were not obviously abnormal in any of these guinea pigs. The lungs of the 2 animals which died were larger than normal, were bright red instead of normal flesh color, and appeared to retain more air than normal guinea pig lungs. About one-third of the killed pig's lungs were involved similarly, but with no apparent order of distribution. The disease was less acute, but quite definite, in a subsequent, nearly identical experiment.

Photographs made of whole and sectioned

[1] From the University of Colorado School of Medicine, Colorado Foundation for Research in Tuberculosis, Denver 20, Colorado.

lungs of affected animals show blebs which may have been caused by the disease induced. Microscopically, these bleb areas have been found to consist of expanded lung tissue in places showing stretched and degenerated alveolar septa and often have been accompanied by a surrounding hyperemic congestion. In any given section from this experiment, about a third of any lobe was affected. Arterial muscular walls appeared thickened and their lumina were often absent. Cursory examinations of sections available to date do not permit even a guess as to what kind of tissue, if any, was destroyed, but gross lung abnormalities were obvious; and the affected guinea pigs are suspected, on the basis of preliminary tests using the Ouchterlony double-diffusion precipitin technique, to have produced circulating antibody against some component of their own lung.

We are now carrying out more extensive experiments on this problem to see whether or not this allergic pneumonitis is related to pulmonary emphysema in the human being, and if so, in what way.

General Discussion

Dr. Loosli: How were the lungs fixed in which you found this pathology?

Dr. Crowle: Some were immersed in formalin, some were fixed by inflating them gently with formaldehyde vapor, and some were fixed in formalin under some vacuum.

Dr. Bukantz: The technique of autoimmunization is perfectly rational. Perhaps the best analogous example would be Freund's production of testicular atrophy by injecting testicular suspensions mixed with adjuvants into elderly guinea pigs or rats. The technique is worthy of exploration.

Dr. Berthrong: An enormous amount of work has been done in attempts to reproduce disease processes with autoimmunization, and a great deal has been claimed for it that has not withstood the test of time. There were a number of papers in which the production of glomerulonephritis was claimed which have not been substantiated. The same applies to encephalomyelitis in rats. Some of the patients with Hashimoto's disease do not have auto-antibodies to thyroid tissue and some do. The original work of Freund is sound and other examples are sound, but it certainly has been overemphasized, in my opinion.

Dr. Crowle: While antibodies have been detected in some cases of Hashimoto's disease, the cause of the disease might be a delayed hypersensitivity rather than autoimmunization.

Dr. Lyons: The guinea pig's shock organ is certainly the lung. Dr. David Long has shown that antigenic and immune processes vary greatly with different species of animals. Therefore, one has to be very cautious in interpreting results in one species as applying to other species. I think Long has shown that the rat is more similar to man than the guinea pig.

Dr. Reeve: I would like to say a few words in favor of immune mechanisms as causes of disease. Witebsky and Rose (J. Immunol., 1956, *76*, 408) showed that rabbits treated with extracts of rabbit thyroid gland suspended in Freund's adjuvant developed antibodies against the thyroid gland proteins, and suffered damage to their thyroids. At about the same time, Doniach and Roitt (J. Clin. Endocrinol., 1957, *17*, 1293) showed precipitins to purified thyroglobulin to be present frequently in the serum of patients with Hashimoto's disease. It seems certain that in rare circumstances tissues may be destroyed by the animal's own immune response to them. How common a cause of disease in man this is, however, remains to be demonstrated by future work.

PEPTIC ULCER AND PULMONARY EMPHYSEMA[1]

W. SILEN, B. EISEMAN, AND W. BROWN

INTRODUCTION

Only recently have clinicians recognized the high incidence of peptic ulcer in patients with pulmonary emphysema. Green and Dundee in 1952 (1) found that 19 per cent of both a clinical and an autopsy series of patients with emphysema had concomitant peptic ulcer. This association of the two diseases was confirmed by Fulton (2) (18 per cent incidence), Lowell and co-workers (3) (24 per cent occurrence), and Latts and associates (4) (20 per cent proved ulcers). In general such ulceration, whether in autopsy or clinical studies has been approximately three times more frequent than in the analogous nonemphysematous controls. A summary of these data is shown in table 1.

The converse statistical approach confirms the frequent coexistence of ulcer and emphysema. Hirvonen (5) reported 34 per cent of clinical patients with ulcer and 39 per cent of autopsy cases to have well-established emphysema. Weber (6) supported this concept by reporting 34 per cent of his series of patients with chronic benign ulcer to have emphysema. These studies indicate that emphysema is two or three times more frequent in ulcer patients than in comparable control subjects.

Approximately 80 per cent of ulcers associated with emphysema are duodenal in location, and apparently have an inordinately great propensity (40 to 50 per cent) for producing serious clinical complications.

REASON FOR COEXISTENCE OF THE DISEASES

Carbon dioxide accumulation: Many factors may be responsible for the frequent occurrence of peptic ulcer in emphysematous patients, but little objective evidence is available in this regard. Browne and Vineberg (7) found that secretion from a total gastric pouch in dogs varied directly with the carbon dioxide content of the blood and was independent of alteration in blood pH. They also noted that the gastric secretion produced by stimulation of the vagus nerves was inhibited by hyperventilation and was restored by raising the carbon dioxide content of the inspired air. Apperly and Crabtree (8) confirmed these findings in fasting adult males, noting direct correlation of gastric secretion with carbon dioxide content of the blood, irrespective of increase or decrease in the pH of the blood. They postulated that the elevated carbon dioxide of the blood displaced chloride ion and made it more available for utilization in the production of hydrochloric acid. Apperly (9, 10) has correlated the incidence of peptic ulceration with environmental temperature, pointing out that ulcer is four times as common in the cool climate of Mackay, North Queenland, as in the tropics of Hobart, Tasmania, despite the fact that the people in both areas are of uniform stock and dietary habits. He postulated that the mild hyperpnea which develops in tropical climates (11) causes a depression of the carbon dioxide content of the blood and thus a decrease in gastric secretion.

Anoxia: Although Van Liere and associates (12, 13) have shown that both the volume and acidity of secretion from Heidenhain and Pavlov pouches of dogs decrease as atmospheric oxygen is reduced, it is unlikely that anoxia per se produces local gastric changes predisposing to peptic ulceration.

Polycythemia: Although polycythemia has been implicated as being significant in causing peptic ulcer, the association is apparently merely on a chance basis (14). Wilbur and Ochsner (14) reported an 8 per cent incidence of peptic ulceration in 143 patients with polycythemia vera, but at the same time questioned the significance of this finding. Apperly and Carey (15) have shown that in man and dogs either a marked elevation or a decrease in hematocrit will diminish gastric acidity. Polycythemia is probably of little importance in producing peptic ulcer in emphysematous patients.

Coexistent psychosomatic factors: It has been suggested that emotional factors may cause peptic ulceration in patients with chronic pulmonary emphysema. Wolf and Wolff (16) point out that hostility and resentment—common

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TABLE 1
INCIDENCE OF PEPTIC ULCER IN PULMONARY EMPHYSEMA

Author	Number of Patients with Emphysema	Number of Emphysema Patients with Ulcer	Incidence of Ulcer	Type of Case
			per cent	
Green and Dundee	64	12	19	Autopsy
Green and Dundee	72	14	19	Clinical
Fulton	42	8	18	Autopsy
Lowell	25	6	24	Clinical
Latts *et al.*	479	74	15.4	Clinical
Latts *et al.*	107	29	27.1	Autopsy

moods in patients with emphysema—result in increased acid secretion, a viewpoint shared by others (5). Gray and co-workers (17) have suggested that the chronic anoxia in a patient with pulmonary emphysema may produce chronic stress, which in turn may cause an excessive adrenocorticotropic response with resultant ulceration.

Much study is needed to assess the relative importance of these various factors in the well-authenticated high incidence of peptic ulcer in patients with pulmonary emphysema. At present, we are investigating the relationship of the carbon dioxide content of the blood to gastric secretion in patients with chronic pulmonary emphysema. Simultaneous twelve-hour night gastric secretions and blood carbon dioxide concentrations are being obtained on patients with emphysema. Detailed pulmonary function tests are being carried out to determine the severity of the emphysema.

SUMMARY

A brief summary has been given of the evidence demonstrating a high incidence of peptic ulceration in patients with pulmonary emphysema. Factors which might be of importance in causing the frequent association of these diseases have been discussed. Current approaches to this problem have been presented.

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GENERAL DISCUSSION

DR. LOWELL: The association between peptic ulcer and emphysema has led us to speculate on the possible role of smoking. We believe that smoking and emphysema are very closely asso-

ciated and that there is an etiologic link between these two things. Perhaps the type of person who indulges in heavy smoking, smoking of a degree to produce emphysema, might also be that type of individual who would be predisposed to develop peptic ulcer.

Dr. H. William Harris (Salt Lake City, Utah): We have had the opportunity of measuring the diurnal blood concentration of 17 hydroxy corticoids and their urinary excretion in a small series of patients with emphysema, one of whom had an active duodenal ulcer. The values in the patients with emphysema and without ulcer were high normal, consistent with other individuals under mild forms of stress. The urinary values were slightly elevated or high normal.

Dr. Gaylord: I am amazed at the report of the frequent association of emphysema with peptic ulcer. In Denver, where we have a good sprinkling of young insurance men and brokers who have a high incidence of peptic ulceration (depending on the state of the stock market), the association with emphysema is very low. In small communities like Burlington or Cheyenne Wells, Colorado, where there is little population left between the ages of sixteen and sixty, the incidence of emphysema is extremely high in all of the patients whom we see, whether they have peptic ulceration or not. Also those areas are quite dusty. In short, I'd like to know where this 40 per cent statistic came from.

Dr. Silen: The large series that I quoted was from Finland.

Dr. Floyd Feldmann (New York, New York): From an epidemiologic standpoint, we do not know the incidence of either one of these diseases; if you're going to compare them, or to postulate that they occur in conjunction with each other, you should indeed be sure you are comparing exactly the same kind of people.

Dr. Silen: In the study from Finland, a control group had one-fourth the incidence of peptic ulcer observed in the emphysema patients.

Dr. Cugell: A disease called progressive scoliosis in children occurs predominantly in young girls. However, in the adult population, thoracic deformity is much more common in males. A significant proportion of these youngsters with progressive scoliosis, whether they have spinal fusions or not, will develop this peculiar business of emphysema and kyphoscoliotic heart disease. Thus, we may have a good group in which to observe the natural history of this disease.

Dr. Fowler: Dr. Krahl thinks he has produced emphysema in rats and would like to be heard.

THE EXPERIMENTAL PRODUCTION OF PULMONARY EMPHYSEMA[1,2]

A PRELIMINARY REPORT

VERNON E. KRAHL

Introduction

Few papers appear on the subject of pulmonary emphysema which do not make some reference to the obscure etiology of the disease. Often the more popular views as to the possible causative factors are reviewed and a preference is expressed for one or more of them. Indeed, it appears highly probable that a multiplicity of factors may be involved which act in concert, but with varying degrees of severity, upon subjects who differ widely in their susceptibilities to the disease. The disease may be expressed in mild, moderate, or severe forms; it may be merely annoying or again crippling; it may progress slowly or with great rapidity, and may be diffuse or localized.

Although the etiologic factors remain to be elucidated, there is little question as to the salient histopathologic features of pulmonary emphysema. The altered histology seen in emphysematous lungs is familiar to the pathologist. Unfortunately, the emphysematous tissues obtained from resected portions of diseased lungs or from those which are removed at post-mortem examination from subjects who have succumbed to the disease are so profoundly altered that little can be determined regarding the initial changes which occurred at the onset of the disease.

It may be assumed that the preliminary changes involve some elements of the supporting framework of the lung. These probably undergo excessive stretching, distortion, and rupture, so that severe damage to the capillary networks, for which they form a scaffolding, ensues. Except for the older, but illuminating studies of Orsós (1, 2), we have little exact knowledge of which of the supportive structures are primarily involved or of the actual sequence of events which convert the fine sponge-work of the normal, healthy lung into the large, thin-walled and physiologically inefficient air spaces, blebs, and bullae which characterize the emphysematous organ.

The realization of the need for an experimental method for the production of pulmonary emphysema as a means of discovering its etiologic factors and of delineating the earliest histologic changes involved has prompted numerous attempts to produce pulmonary emphysema in the laboratory. A detailed account of the various methods which have been tried is beyond the scope of this paper. Some methods have been mentioned by Doctor Eiseman in his paper on experimental emphysema (3). References 4 to 22 of the present article may serve as an introduction to the pertinent literature, but they do not represent an exhaustive coverage. Techniques employed in the past include surgical removal of portions of lung, constriction or obstruction of airways, and a reduction of oxygen in the air breathed by experimental animals. Most of the experiments have failed to produce emphysema or have given inconclusive results. Some of the writers have not used adequate controls; others have failed to give a sufficiently clear description of the histologic findings to permit an evaluation of their results. A good historic review and a critical analysis of the earlier attempts to produce pulmonary emphysema have been published by Paine (21).

Commonly reported in the histories of patients having pulmonary emphysema are asthma or chronic bronchitis and a chronic cough, frequently combined with increased bronchial secretions. Transport of air through the respiratory tree requires great effort on the part of the subject, particularly in the expiratory phase of the respiratory cycle. It has been assumed, therefore, that important etiologic factors in pulmonary emphysema are the distending forces created in the peripheral airways by coughing or simply by forcible expiration through inflamed, narrowed passages which may be intermittently blocked by plugs of thickened secretions. The frequent mention in the literature of a check-valve or ball-valve mechanism as a possible explanation of

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air trapping and difficult expiration in emphysema suggested the experimental method employed in the present study, namely, the installation of ball valves in the airways of the experimental animals.

Although the notion of obstructing expiratory flow by the introduction of a valve into an airway occurred independently to the writer, a search of the literature soon showed that it was by no means a novel idea (11, 12, 19, 21). The valve or other obstructing device used in the earlier studies usually has been placed in the trachea, whereas the respiratory blockage in bronchitis or bronchiolitis (which is probably one of the underlying factors in pulmonary emphysema) is located farther peripherally. For this reason the sites chosen for the valves in the present study were as far peripheral in the lungs as possible, namely, in lobar bronchi or in some of their branches.

Materials and Methods

Animals: The animals used in this experiment were healthy adult male albino rats, weighing approximately 400 gm. each.[3] In each of 12 animals a plastic ball valve was placed in the lower right lobe bronchus. Two rats served as unoperated controls. In addition, each experimental animal provided control tissue from the intact lobes of its own lungs. In each case a piece of control tissue was excised from the caudal portion of the left lung at a position corresponding to that of the block of experimental tissue taken on the right.

Ball valves: Valves were made of short pieces of polyethylene tubing,[4] about 5 mm. in length, in stock sizes P.E. 190 and P.E. 200 (outer diameters: 1.7 mm. and 1.9 mm., respectively). Valves of these diameters slipped easily down the trachea and fitted snugly into lobar bronchi or some of their more peripheral branches. The valve seats were rings cut from smaller sizes of tubing (P.E. 90 for valves of P.E. 190, and P.E. 100 for valves of P.E. 200). Steel balls of suitable size were obtained from the tips of ball-point pens. The ball was prevented from escaping from the "open" end of the valve by 2 or 3 small internal projections made by dimpling the outer surface of the tubing with a warm needle point (figure 96).

Installation of the valve: A polyethylene cannula or director was passed through a small tracheotomy opening in a nembutalized rat and was advanced into the right main bronchus or into the right lower lobe bronchus. If the cannula and the valve to be used were of the same diameter, then the most peripheral point to which the cannula's tip could be advanced was the point at which the valve would later come to rest. (Before its withdrawal the cannula may be marked where it protrudes from the trachea and thus serve as a gauge of the depth and general location of the valve. In 4 cases the locations of the valves were ascertained accurately in roentgenograms.) A long, flexible needle (piano wire; sharpened and drilled) was passed through the cannula. After traversing the tube the needle passed through the peripheral parts of the lung, body wall, and skin. The cannula was removed, leaving the needle in place. The latter was threaded with 7-0 silk or, preferably, a long hair (hair produced less local irritation of tissues) which was tied to the leading or "open" end of the valve. Then, as the needle was withdrawn through the body wall, the valve entered the trachea, followed the course taken by the cannula, and came to rest at the predetermined point in the bronchus. The valve was anchored by stitching its "tow-line" to the subcutaneous tissues at the needle's point of exit. In this initial experiment the valves were left in place for periods varying from two to twelve weeks.

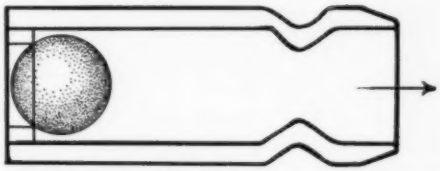

FIG. 96. Diagram of ball valve. Body and seat of valve are pieces of polyethylene tubing; steel ball is obtained from a ball-point pen.

The animals survived the operation well. Aside from occasional "wet" grunts and wheezes which were heard for the first day or two following placement of the valve (possibly a result of tracheobronchial trauma during passage of the valve) the rats gave no further visible or audible evidence of respiratory difficulty.

Removal of lungs, fixation, and staining: The thorax of the nembutalized rat was opened quickly. A ligature was placed about the great vessels to prevent exsanguination of the lungs, and the heart was removed. Then, lungs, trachea, and larynx were removed and Zenker-formol solution was introduced through a tracheal cannula. The fixative was permitted to enter by gravity until the lungs had regained their normal size and contours. The trachea was tied, and the entire preparation was immersed in fixative overnight. When the lungs were carried to 70 per cent alcohol, a block of tissue containing the valve was removed and a piece of normal lung from a corresponding area of the opposite side was taken as a control sample. The block containing the valve was divided into two parts so that the

[3] Rats of the SS-MP strain were obtained from Supplee Division, Foster D. Snell, Inc., Bainbridge, N. Y.

[4] "Intramedic" polyethylene tubing, medical formulation, PHF; Clay-Adams, Inc., N. Y.

valve might be removed prior to sectioning. In most cases the valve was clean and unoccluded upon removal. Serial sections were made at 10μ and 50μ. Alternate slides were stained with hemotoxylin and eosin and with orcein and methylene blue.

Observations

Gross appearance of lungs: When lungs were examined at autopsy, it was commonly noted that the lower right lobe of the lung, particularly in its caudal portion, did not collapse as completely as the other lobes. In each case the silk or hair which had been used to anchor the valve emerged through the lung's surface at or near the sharp margin which separates the costal and diaphragmatic surfaces of the lobe. An area of lung surface from 0.5 to 1 cm.^{2} immediately surrounding the hair or silk had a dark red color like that of liver. Upon the basis of shape and sharp demarcation from the adjacent lung tissue, the dark area is considered to represent the subpleural base of a secondary pulmonary lobule. Adjacent to this and varying from a narrow band of tissue to as much as one-half of the lower right lobe an area was usually found which differed distinctly in color and consistency from both the darker area and from normal lung. It was much lighter in color, contained unusually large air spaces, and did not collapse as much as the normal portions of the lung.

Microscopic appearance of the lungs: Lungs which have been restored to their normal degree of distension by the tracheal instillation of fixative differ microscopically in several respects from those usually seen in laboratories of histology or pathology. Accordingly, a brief description of normal rat lung, redistended by fixative, may be appropriate. Figure 97 is a photomicrograph (× 100) of normal rat lung which will serve as a basis of comparison with other, experimentally altered lungs, fixed in the same manner and shown at the same degree of magnification in subsequent figures.

When lungs contract upon the opening of the thorax there is a decrease in the average diameter of alveoli of approximately 30 per cent. A further reduction of as much as 12 may occur upon fixation. If pieces of collapsed lung are excised at autopsy and fixed by immersion, a variable amount of additional distortion occurs which is somewhat dependent upon technique and sharpness of instruments.

Unlike the deep, narrow alveoli which are characteristic of sectioned collapsed lung, those in normally distended lungs have relatively wide mouths and walls which diverge from each other to meet the base which, therefore, is wider than the mouth. The bases are usually conical so that those bases which form the common wall between two adjacent alveolar ducts describe a zigzag line. These zigzag lines are a common feature of sections of normal lungs (23), whether collapsed or distended, but are more obvious in the latter state. The characteristic zigzag line formed by the dovetailing of alveolar bases is well shown in figure 97, extending downward from above center to left of center in the photomicrograph.

Whereas the interalveolar septa of collapsed lungs appear wavy and irregular in sections, they tend to be straight or flat in distended lungs like the walls of the compartments of a honeycomb or of soap bubbles which are confined within a container. As a result, sections of a distended lung will display a far greater number of interalveolar septa which have been taken in the plane of section, so that their capillary networks, alveolar pores, and other features may be easily examined.

In distended lungs, alveoli which are cut in planes which pass through the open mouths usually show a small knoblike enlargement at the tip of each interalveolar septum. The enlarged tip contains the cross-section of muscle, and elastic and collagenous fibers which lie in the entrance ring of the alveolus. Many entrance rings cut in this way are seen in sections of distended lungs, for the wider, more shallow alveoli of the distended lung tend more frequently to be cut in a plane which passes through the open alveolar mouth, and this gives a preponderance of open or U-shaped outlines. On the other hand, collapsed lungs, in which alveoli have a more elongated form, show far more instances in which the plane of section passes across the alveolar lumen. As a result, there is a predominance of closed or O-shaped alveolar outlines in preparations of collapsed lungs.

Experimentally altered lung tissue: In the immediate vicinity of the ball valve there was evidence of a mild inflammatory reaction. Connective tissue surrounding the bronchus was somewhat edematous, and lymphoid tissue in the walls was hypertrophied. Especially in cases in which the valve fit rather loosely in the bronchus, the

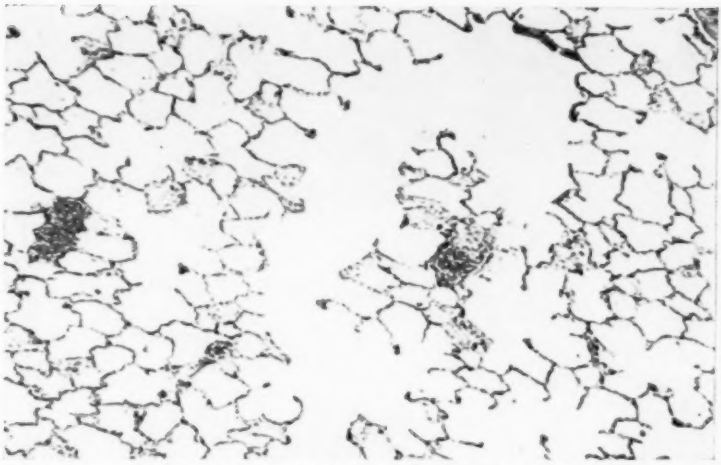

FIG. 97. Section from unoperated (control) left lung of a rat. This area of normal lung tissue is magnified to the same degree as the sections seen in subsequent figures and serves for comparison of alveolar size, length of interalveolar septa, et cetera. (Fixation: Zenker-formol solution, instilled intratracheally, × 100) (For further description, *see* text).

bronchial epithelium appeared flattened, stratified, and had lost its cilia.

The dark red, liver-like area at the caudal pole of the lower right lobe proved to be atelectatic upon microscopic examination. The collapsed alveoli contained variable quantities of fluid and numerous phagocytic cells. These alveoli, alveolar sacs, and alveolar ducts constituted the more peripheral branches of the portion of the respiratory tree which contained the valve. Moreover, the hair or silk which served to anchor the valve invariably made its exit through this atelectatic portion of the lung. It appears likely that the combined effects of loss of ciliary activity at and near the valve, increased secretions of irritated epithelium, and the local irritation of lung parenchyma by the hair or silk brought about a complete blockage of this lobule with the subsequent resorption of its air. However, just proximal to this area of atelectasis and for a variable distance surrounding and peripheral to the ball valve the lung tissue contained many abnormally large air spaces.

An area is shown in figure 98 near the thin edge of the lower right lobe of a lung in which a ball valve had lodged for eighteen days. In a comparable normal area, one would expect to find airways no larger than terminal bronchioles or alveolar ducts. Yet, in this experimentally altered lung the air spaces are relatively huge and irregular. From their general configurations and the presence around their periphery of greatly shortened and degenerating interalveolar septa, it may be inferred that these were originally alveolar ducts and alveolar sacs. The zigzagging of the common boundaries between adjacent airways has been lost. In some locations interalveolar septa have disappeared; some are reduced to small, rounded knoblike projections along the walls of the enlarged space; others are markedly shortened and are *T*-shaped, i.e., they are surmounted by a flat cross-piece in place of the slight enlargement commonly seen at the "free" ends of interalveolar septa. When stained selectively for elastica by orcein, the cross-members of the *T*-shaped septa show a concentration of elastic fibers. On the left in figure 98, the partition between two greatly enlarged alveolar sacs contains an accumulation of elastic fibers which must originally have supported interalveolar septa but which are now arranged in parallel layers. The interalveolar septa have disappeared completely along this partition.

Figure 99 is a photomicrograph of an area of lung tissue located peripheral to the position of a valve in the lower right lobe bronchus. This valve had been left in place for about ten weeks. The field is dominated by unusually large, thin-

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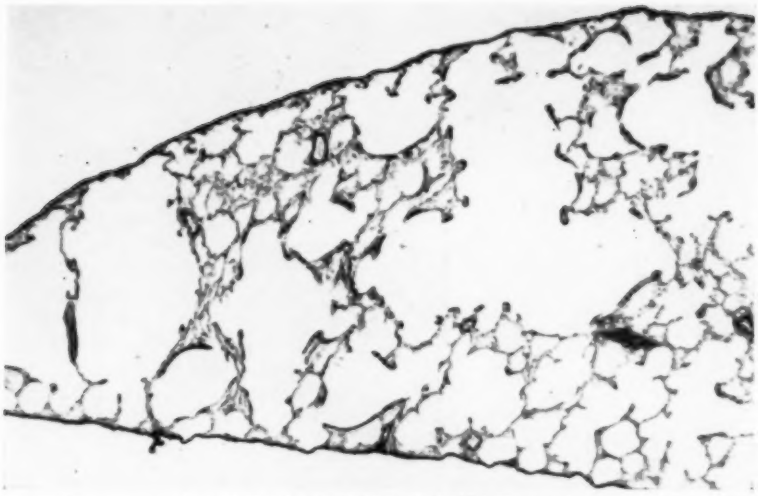

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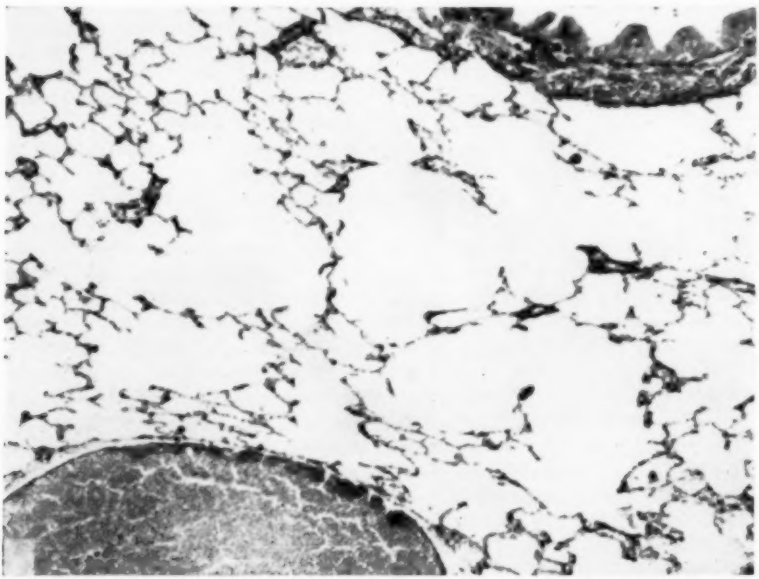

FIG. 98. Section from the operated, right lung of the rat used in figure 97. This area near the caudal tip of the right lower lobe exhibits emphysematous changes. The tissue was located distal to the position of a ball valve installed in the right lower lobe bronchus. Toward the right of the section, note shortening of interalveolar septa, clubbing and flattening of tips of septa. On the left, near tip of section, extreme shortening of some interalveolar septa and complete loss of others have occasioned the coalescence of numerous alveoli and the production of abnormally large air spaces. Duration of experiment, eighteen days. (Orcein-methylene blue, × 100)

FIG. 99. Alterations in an area of lung distal to a ball valve placed in the right lower lobe bronchus. Duration of experiment, seventy-one days. There is some shortening and disappearance of interalveolar septa with a consequent enlargement of air spaces. Note the partial loss of the characteristic zigzag arrangement of alveolar bases (compare with figure 97). (Zenker-formol solution, instilled intratracheally; orcein-methylene blue, × 100)

walled air spaces. Remnants of interalveolar septa of various lengths are seen at irregular intervals around the periphery of these spaces. Comparison of this illustration with figure 97 (both at 100 ×) emphasizes the marked shortening of interalveolar septa and the complete loss of the typical zigzag configurations which have occurred.

An area of even greater destruction is illustrated in figure 100*A* in a lung which had carried a valve for about ten weeks (compare with figure 97). Most of the large, thin-walled cavities represent former alveolar sacs whose surrounding alveoli have suffered a severe degeneration or disappearance of their interalveolar septa. Where interalveolar septa persist they are much shorter than normal, and many are distinctly clubbed or *T*-shaped. The two elongated airways probably

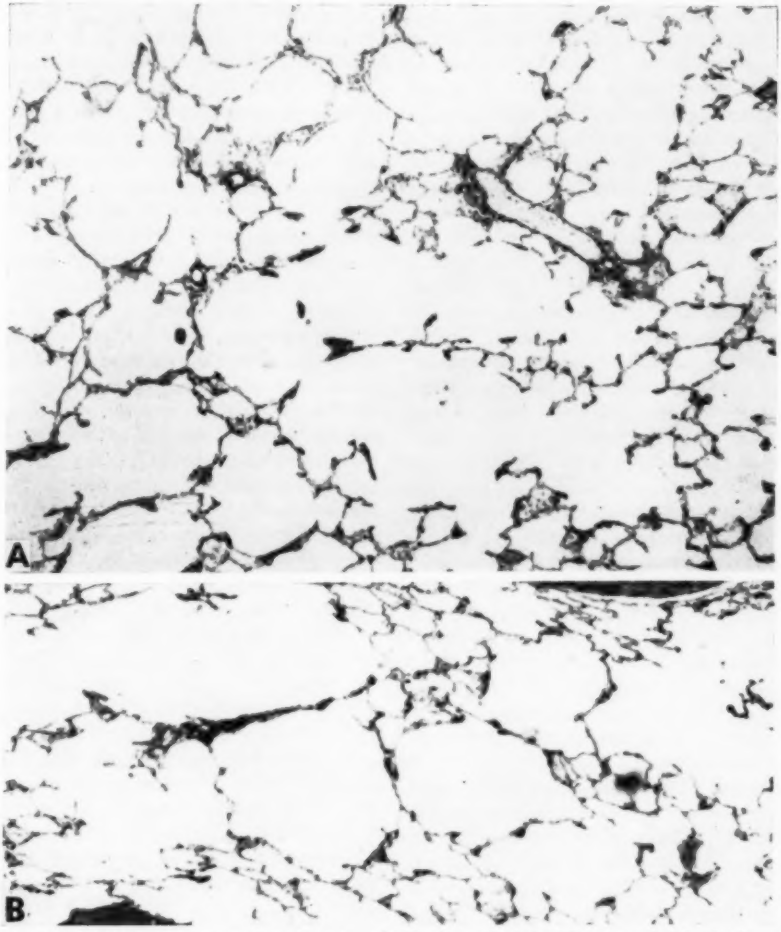

FIG. 100*A*. Section from an area of rat lung near ball valve which had been carried in the lower right lobe bronchus for seventy-one days. Only a few alveoli in this field are of normal size. Widespread degeneration and disappearance of interalveolar septa with the production of large, irregular spaces may be noted. (Orcein-methylene blue, × 100) *B*. Section from a more distally located block of tissue of the same right lower lobe. Only a few vestiges of interalveolar septa remain in most areas. The normal zigzag pattern of alveolar bases has largely disappeared. (Zenker-formol solution, instilled intratracheally; hematoxylin and eosin, × 100)

represent alveolar ducts. The partition between them still bears a few irregular remnants of interalveolar septa, but has lost its characteristic zigzag arrangement. In Figure 100*B*, which shows an area peripheral to that seen in 100*A*, nearly all interalveolar septa have been lost.

In all such damaged areas of the lungs, examination at higher magnification reveals a distinct attenuation of the walls of the air spaces, a diminution in the number of elastic fibers, a concentration of torn and retracted elastic fibers in the persisting partitions, and a decreased vascularity of the partitions between the remaining airways. Although somewhat milder in degree, these changes bear a remarkable resemblance to those found in the emphysematous lungs of human subjects. At the margins of these experimentally altered fields, grades of damage intermediate between these and completely normal lung may be found.

Discussion

The experimental method outlined above produces alterations in lung tissue which resemble in many respects those which are characteristic of emphysematous lungs. These changes include the rupture, retraction, and rearrangement of elastic fibers in the airways which lie peripheral to the ball valve, retraction (shortening) of interalveolar septa, loss of the characteristic zigzag patterns described by the alveolar bases, enlargement of the central lumina of alveolar ducts and alveolar sacs at the expense of alveolar depths, clubbing of the tips of interalveolar septa as seen in sections, complete disappearance of many septa, and the coalescence of adjacent air spaces into abnormally large ones.

The presence of a ball valve in a lobar bronchus produces airtrapping and increased pressures within the peripheral branches of the lobe. At the same time, inflammation frequently occurs in bronchi and bronchioles distal to the valve. Both air trapping and inflammation are thought to be important etiologic factors in pulmonary emphysema (*see* the series of papers by McLean on bronchiolitis and pulmonary emphysema (25–31). Persistent overdistension of the air spaces leads ultimately to a destruction of elastic and other supporting elements of their walls. Once elastic fibers begin to rupture and retract, then the other structural changes listed above become increasingly apparent.

The dense interweaving of elastic fibers in the wall of an airway and of those, in turn, with the fibers of adjacent airways, arteries, veins, and visceral pleura has been well demonstrated (1, 2). The important role of this elastic "continuum" in the maintenance of support and normal contours of the airways was stressed by the writer earlier in this conference (24). The shape of the alveolus and of its entrance ring, the patency of the smaller airways which lack cartilaginous supports, and the zigzag lines formed by shared alveolar bases are all dependent upon the integrity of the fibrous scaffolding of the lung.

The results of the present study and of other works, when combined with our knowledge of the histopathologic changes which are seen in later stages of pulmonary emphysema, permit us to piece together the following account of the natural history of the disease. The site of the original damage which leads directly or indirectly to all further steps in the development of emphysema appears to be in the small bronchus or bronchiole. A decrease in the caliber of these air passages, whether by inflammatory thickening of their walls, edema, enlargement of adjacent lymphoid tissue, or by excessive contraction of smooth musculature, impedes the flow of air through them in either direction, but does so especially during expiration. The increased radial traction exerted by elastic fibers upon the smaller airways during expansion of the lungs may be sufficient to hold them open despite an inflammatory narrowing. On expiration, however, the reduced traction plus mural swelling so reduces the diameter of the lumen as to seriously hamper or prevent the expiratory flow of gases. Increased glandular secretory activity adds to the difficulty by introducing a physical obstruction into the airway. A ball-valve mechanism is then established which subjects peripheral air spaces to excessive pressures and overdistension with each expiratory effort. Frequent and strenuous coughing is particularly damaging to interalveolar septa. When the degree of distension exceeds the elastic limits of fibrous supporting elements in the walls of airways, the fibers rupture and retract.

An immediate result of the rupture of elastic fibers of alveolar entrance rings and of interalveolar septa is a sagging and relaxation of these septa. Consequently the interalveolar septa become shorter and their tips, as seen in cross-sec-

tion, become clublike by reason of the retraction of broken elastic and other fibers. With the regression of septa, the lumina of alveolar ducts and alveolar sacs increase in diameter (thereby reducing the total surface area). Since the patency of the smaller air passages, particularly in the expiratory phase of the respiratory cycle, is critically dependent upon the radial tension exerted by the elastic fibers, the loss of the latter carries with it serious consequences. As more and more elastic fibers are broken, the progressive loss of tension upon the walls of neighboring bronchioles, et cetera, fosters expiratory narrowing or collapse. Such collapse may occur then in nearby airways which were not involved in the original, localized inflammation. The instances of air trapping are multiplied in this way with similar consequences, namely, the overdistension of the peripheral air spaces and loss of additional elastic fibers. As abnormally large spaces arise through the loss of interalveolar septa and such spaces coalesce to form still larger ones, the blebs and bullae characteristic of emphysematous lungs are formed.

These balloon-like spaces contribute to the respiratory embarrassment of the subject in a variety of ways. Their linings are inefficient as respiratory surfaces. Moreover, air enters more readily into these large, inelastic cavities than into the smaller, more resilient spaces of the remaining normal areas. The intrathoracic volume occupied by the emphysematous tissue is no longer available to the remaining useful lung tissue for its expansion. Finally, large imperfections in the fibrous framework of the lung result in a diminution in the radial elastic tension upon which the bronchioles are dependent for their patency and so, expiratory collapse and air trapping are perpetuated.

With respect to the pulmonary circulation, the consequences of the loss of elastic fibers are equally serious. As elastic and collagenous fibers are lost, the interalveolar capillary networks (which are the principal constituents of the septa) become progressively stretched. Only a slight attenuation is required to retard or halt the passage of blood cells through the pulmonary capillaries. The fine networks of reticular fibers about the capillaries constitute their only remaining means of support, but such fibers lack the elastic resiliency and strength necessary to withstand the continued excessive tensions and so they, too, break down. Capillaries then rupture, retract, and disappear. As this vascular bed is reduced in size, so is the volume of blood which may be brought in a given period of time to the respiratory surfaces for gas exchange. Furthermore, the capillary attenuation and the over-all decrease in volume of the capillary bed result in an increased resistance in the pulmonary circuit and an elevation in pulmonary arterial pressure which, in time, is reflected in structural and dynamic changes in the right side of the heart.

With the technique employed in this study and within the relatively short duration of the experiments, the emphysema-like alterations of the lungs do not proceed to the extreme pathologic states seen in far advanced cases of emphysema in man. However, by the same token, the method provides a means of studying the earlier structural changes which occur during the development of this condition and which, therefore, are not as well understood as the later ones.

While the observed changes resulting from the installation of ball valves in the airways lend support to the belief that air trapping is an important etiologic factor in the development of pulmonary emphysema, they do not preclude the possibility that other—perhaps equally important—factors may be involved (for example, the repetitive and explosive forces developed in the coughing which accompanies chronic bronchitis).

Inasmuch as this paper is presented in a session devoted to experimental studies and avenues of investigation, it may be appropriate to suggest a few further methods of approach to the question of the etiology of emphysema. There is good evidence (25–31) that the seat of origin of the inflammation and air trapping leading to pulmonary emphysema lies peripheral to the bronchi; namely, in the bronchioles. Air-borne irritants, such as industrial dusts and fumes and tobacco smoke, have been mentioned as possible factors in producing inflammation of the airways. Therefore, experimental animals might be subjected to a wide variety of irritating substances in various concentrations as a means of producing bronchiolitis and, presumably, air trapping. Inflammation and hypersecretion by glandular elements of the airways might be achieved by the introduction of various bacteria into the respiratory tree. Airways might be narrowed by a variety of methods, including the introduction of allergens (experimental asthma), and by stenosis

through the application of caustic substances. Physical blockage of the smaller airways could be produced by the administration of drugs which would increase either the quantity or viscosity of glandular secretions. Removal of secretion products could be hampered by any agents which would reduce or eliminate the motility of tracheobronchial cilia. When the individual effects upon the lung of coughing, bronchial and bronchiolar narrowing, inflammation, hypersecretion, smooth-muscle contraction, destruction of elastic fibers, and other factors presumed to be important in the etiology of pulmonary emphysema have been determined in this way, the next step obviously would be to plan experiments which would superimpose these effects in various combinations.

Summary

A technique is described by which a ball valve may be installed in a bronchus of the rat's lung. The valve offers resistance to expiratory air flow and produces local irritation and inflammation of the airway. After carrying a valve in the right lower lobe bronchus for periods from eighteen to seventy-one days the lungs of experimental animals show grossly discernible, localized differences in color, degree of distension of peripheral airways, and tendency to collapse.

Microscopic examination of lung tissue located peripheral to the position of the valve reveals a general increase in the diameters of peripheral airways, the degeneration of interalveolar septa, and the formation of abnormally large air spaces. Experimentally altered tissues which are stained selectively for elastica reveal marked alterations in the quantity and arrangement of elastic fibers.

The principal changes which have been noted are a loss of the normal zigzag configurations described by alveolar bases shared by the alveoli of adjacent alveolar ducts, alveolar sacs, et cetera. There is a retraction or shortening of interalveolar septa with clubbing or flattening of their tips and a final disappearance of many septa. The loss of interalveolar septa and the coalescence of adjacent air spaces lead to the formation of abnormally large, irregular, thin-walled airways. These alterations in pulmonary tissue are interpreted as results of increased resistance to expiratory air flow and, possibly, of irritation and inflammation. It is suggested that they represent some of the structural changes which occur in lungs during early stages in the development of pulmonary emphysema.

Several experimental approaches, designed to further elucidate and identify the etiologic factors in pulmonary emphysema are mentioned.

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General Discussion

A physician: How long were the experiments?

Dr. Krahl: In the first series the duration of the experiment was a little over two weeks, and in the last series a little over two months.

Dr. Fowler: Old rats develop emphysematous changes peripheral to the development of lymphoid nodules. That led me to obtain and keep some old rats. They got sick, and wheezed and died, but they didn't have typical emphysema.

Dr. Krahl: I've never seen it occur in any of the rats that I have, but I have heard from others that, in certain strains at least, it may occur spontaneously in older animals.

Dr. Loosli: I had an opportunity to study the development of the lung through thirty to one hundred and twenty days in a strain of rats. As the animals became older, chronic infection appeared; some of the lungs became atelectatic, but the remaining lung remained patent, and some showed simple hypertrophy. It was not true emphysema in these animals, even in the very old ones.

Dr. McLean: In the rats that I used, in which I tried to produce emphysema experimentally, spontaneous bronchiectasis affected almost all of them. The origin of this condition in rats is to my mind a bronchiolitis which causes progressive bronchiolar obliteration. Grossly, you can see patchy atelectasis and large dilated bronchi which can in the final stages become huge things packed with mucus, almost the size of a rat lobe. On occasions, in the periphery of these damaged bronchi, I found my histologic emphysema, i.e., evidence of destruction of the normal anatomy. I think this is quite different from the condition Dr. Krahl has produced. He has produced "emphysema" without producing any gross change in bronchial anatomy in the rat. When I talked to him about his work, he was good enough to admit that it was highly probable—in fact almost essential to his experiment—that there was an inflammatory process going on along with this ball valve. I also asked him if he could possibly repeat this experiment using a similar mechanism but without a valve. I consider it is the action of the foreign body rather than its valvular action which has produced this change.

Dr. Eiseman: At least six people who have used ball valves in the past have taken the balls out and have found the same picture. In other words, some people, at least, claim that it is just the infection.

Dr. Liebow: It is possible to produce a tremendous degree of obstruction locally with overdistention to an extent where capillaries may be compressed because of the pressure within that localized region. If one attempts to do this on a generalized basis, obviously no animal or man would survive.

Dr. Mitchell: Hans Grüneberg described a strain of rats in 1938, of whom 50 per cent died of "emphysema" and/or cor pulmonale some thirty

to forty-five days after birth (Grüneberg, H.: An analysis of the pleiotropic effects of a new lethal mutation in the rat (Mus norvegicus), Proc. Roy. Soc. Biol., 1938, *125*, 123). A year later he reported that the lungs were primarily, not secondarily, enlarged and therefore not emphysematous after all (Fell, H. B., and Grüneberg, H.: The histology and self-differentiative capacity of the abnormal cartilage in a new lethal mutation in the rat (Rattus norvegicus), Proc. Roy. Soc. Biol., 1939, *127*, 257). He did add, however, that some of the rats weren't able to breathe through their nostrils because their nostrils were full of rubbish from the nest, and they weren't able to sneeze because they didn't have the power; apparently, therefore, many of them died of inanition because they couldn't eat and breathe at the same time. In spite of his doubts, this sounds like true emphysema and is traceable to abnormally soft costal and tracheobronchial cartilages.

CLINICAL ASPECTS OF EMPHYSEMA

H. William Harris, *Moderator*

THE NATURAL HISTORY OF EMPHYSEMA IN MAN[1]

RICHARD EBERT

In describing the natural history of a disease it is first necessary to establish a definition. In defining a disease we classify a group of patients into a category on the basis of one or more common characteristics. Once this group of patients has been so classified, the clinical symptoms and course of the disease can be described.

The problem in emphysema lies in the area of definition of the disease and hence classification of patients. If the records of any hospital are scanned, it will be found that the term emphysema is often loosely used and applied to a diversity of clinical problems. Hence, to give any coherent account of the clinical course of the disease, a rigid definition must be established.

The traditional method of classification of emphysema is based on clinical-pathologic correlation. The classical description of Laennec is an example of this approach to the problem. This method has severe limitations. The pathology of emphysema is not an all or none phenomenon. One can state with some assurance that a patient has or has not bronchogenic carcinoma if the lung is carefully examined. Similarly if one defines pulmonary tuberculosis as the presence of tubercle bacilli in the lung associated with an appropriate reaction, the presence or absence of this disease can be established with some reliability. In the case of emphysema the degree of change in the lung can be quite variable. In some lungs, a few bullae or dilated air spaces may be present. In others, both lungs may be almost entirely replaced by bullae of various sizes. In this regard emphysema is similar to arteriosclerosis in that the pathology must be defined quantitatively as well as qualitatively.

There are other problems related to the pathologic definition of emphysema. Most pathologists do not fix the lungs in an inflated state. Hence, the gross and microscopic evaluation of the disease lacks precision. Recently Gough has described a centrilobular form of emphysema. This could readily be overlooked on routine autopsy examination. Another problem in the correlation of the clinical with the pathologic findings in emphysema is that the roentgenogram does not accurately mirror the pathologic process. In many of the diseases of the lung the pathologic process is accurately reflected in the roentgenogram. As a consequence, we are able to constantly make clinical pathologic correlations. In emphysema this type of correlation is not possible and we must await the death of the patient for an accurate appraisal of the pathologic changes in the lung.

For the reasons just mentioned clinicians have begun to rely more and more on a physiologic definition of emphysema. Unfortunately, the data are not available to precisely correlate this physiologic definition of the disease with the pathologic definition. The difficulties of such a correlation are evident and involve the temporal relationship between the physiologic studies and the death of the patient. Nevertheless data which would permit such a correlation are desperately needed.

In view of the difficulties attendant on the diagnosis of emphysema, I shall first attempt to describe the clinical course of patients with typical diffuse hypertrophic or obstructive emphysema. In essence this differs little from the original description of Laennec. Later, I shall discuss patients presenting a less typical clinical picture and certain closely related clinical entities.

The chief symptom of emphysema is dyspnea. Characteristically this begins as exertional dyspnea. The patient notes that his activity is being limited because of shortness of breath. Each month or year he finds that he can accomplish less. Often the symptom develops in such an insidious manner that the patient attributes his limitation of activity to aging or loss of physical fitness. As the disease progresses, the patient often finds he cannot accomplish his usual work. If he is a manual laborer, he may

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find that he has to stop work entirely. Finally the patient reaches a stage where he is unable to walk even a short distance without being tortured by dyspnea. In addition to exertional dyspnea, the patients often have more severe episodes of dyspnea occurring at rest and often accompanied by wheezing. The patient may refer to these attacks as "asthma." These acute episodes are usually precipitated by an upper respiratory infection and often are accompanied by an increased production of sputum. It is thought that these attacks are caused by an exacerbation of the chronic bronchitis which is present in most patients with emphysema. Certainly, administration of adequate amounts of antimicrobial drugs usually gives dramatic relief.

Cough is a persistent symptom in most patients with emphysema. It may antedate or follow the onset of dyspnea. The degree of production of sputum is extremely variable. Some patients may produce only a small amount of mucoid sputum while others may produce large amounts of purulent sputum. The sputum production is greatest following a respiratory infection.

Many patients with emphysema have a slight decrease in the oxygen saturation of the hemoglobin of the arterial blood and a slight increase in carbon dioxide tension. A few patients are markedly cyanotic and exhibit a marked decrease in oxygen saturation of the hemoglobin at all times. There appears to be little correlation between the degree of hypoxia and the severity of the dyspnea. Some patients will have marked dyspnea and little hypoxia and others marked hypoxia and only moderate dyspnea. Polycythemia is rather uncommon in emphysema and may be absent even in patients with severe hypoxia.

The most serious threat to the life of the patient with emphysema is the sudden increase in hypoxia and hypercapnia which accompanies an exacerbation of the bronchitis. The patient may note a preceding acute upper respiratory infection or this may evade his attention. He has a sudden increase in dyspnea and becomes cyanotic. Often he becomes disoriented and confused. Cough may be absent or ineffective, and secretions accumulate in the trachea and bronchi. Fever may be present or absent. Administration of oxygen may lead to improvement, or the patient may lapse into coma as a result of an increase in carbon dioxide tension in the arterial blood and resultant respiratory acidosis. Death may occur if treatment is not prompt and effective.

Evidence of right heart failure is commonly found in these patients. The severe hypoxia apparently leads to an exacerbation of the previously existing pulmonary hypertension. The pulmonary hypertension together with the effect of hypoxia on myocardial function appears to be responsible for the failure of the myocardium. The manifestations of right heart failure include cardiac enlargement, elevated venous pressure, hepatomegaly, and edema. There is no evidence to indicate that the right heart failure adversely influences the function of the lungs as the pulmonary capillary pressure has been normal in those instances in which it has been measured. The heart failure is usually not chronic in nature but clears when the acute bronchial infection subsides and the hypoxia improves.

The prognosis of emphysema in terms of mortality is not well defined. In part this is related to difficulties of classification and definition. A recent study by Bates, Knott, and Christie of patients with typical emphysema is helpful. They observed 59 patients over an average period of three years. During the period of observation, seventeen patients died. Diffusion capacity correlated best with prognosis of the pulmonary function tests studied.

In considering the natural history of emphysema, we must admit that there are a number of patients who do not follow the classical clinical course just given, but who are usually considered to have emphysema. A similar problem is encountered in other diseases of obscure nature.

One of the controversial aspects of emphysema is its relationship to bronchial asthma. A number of patients with typical emphysema will give a previous history of bronchial asthma. Often this history is not easy to interpret. The episodes of dyspnea accompanying acute bronchial infection in emphysema are difficult to differentiate from true bronchial asthma. However, in a number of patients, episodes of dyspnea and wheezing precede the clinical picture of emphysema by many years. The incidence of pulmonary emphysema in patients with bronchial asthma is also difficult to establish. The problem is accentuated by the impossibility of clearly differentiating bronchial asthma from pulmonary emphysema by pulmonary function studies if bronchial obstruction

is present. Certainly, many patients with bronchial asthma have no evidence of emphysema clinically or pathologically. Gough studied the lungs of seventeen patients who died of bronchial asthma. Evidence of emphysema was found in only one, and this was associated with severe bronchiectasis. The relationship between bronchial asthma and emphysema needs further clarification.

A similar problem exists in the relationship between chronic bronchitis and emphysema. It is clear that chronic bronchitis is often associated with pulmonary emphysema and that acute bronchial infection precipitates the more severe episodes of dyspnea and hypoxia. A more controversial point is whether emphysema is preceded by chronic bronchitis in the great majority of patients with emphysema. This depends largely on the determination from the history as to whether a chronic cough preceded the onset of dyspnea. Often this is difficult to establish clearly. In general, British authors emphasize that chronic bronchitis precedes almost all instances of pulmonary emphysema, whereas American authors place much less emphasis on this point. Whether this is related to an actual difference in the incidence of bronchitis in the two countries is not entirely clear. Certainly the diagnosis of uncomplicated chronic bronchitis is made less often in this country than in Britain.

There also appears to be a relationship between bronchiectasis and emphysema. I am not referring to the mild cylindrical dilatation of the bronchi found on the bronchograms of many patients with emphysema or to small focal areas of emphysema adjacent to the dilated bronchi or areas of fibrosis on pathologic examination of the lungs in severe bronchiectasis. Rather I have reference to certain patients with diffuse emphysema who have the findings of saccular bronchiectasis and in whom the bronchiectasis preceded by some years the symptoms of emphysema. Moreover, a number of patients with severe bilateral bronchiectasis develop pulmonary insufficiency. In some of these patients, the roentgenographic picture and pulmonary function studies suggest pulmonary emphysema as the predominant factor in the impairment of pulmonary function rather than pulmonary fibrosis. There also appears to be an undue incidence of diffuse pulmonary emphysema complicating other chronic inflammatory diseases of the lung, particularly if these diseases involve both lungs diffusely and are associated with pulmonary fibrosis. Emphysema may also complicate silicosis. A focal type of emphysema has been described in the lungs of coal miners by Heppleston.

The term senile emphysema has been defined in such various manners that it would not appear to be useful. Certain changes in pulmonary function occur with aging. There is a decrease in vital capacity and an increase in residual volume. In association with these changes in lung compartments, there is a change in the elastic properties of the lungs. In contrast to diffuse emphysema, there is no alteration in resistance to expiratory air flow nor is there a marked change in distribution of inspired gas. These elderly persons have no respiratory symptoms. If such persons develop bronchitis with obstruction to air flow, the physiologic findings could readily be confused with those of emphysema.

The barrel-chest phenomenon should be mentioned because of the confusion to which it has led in the clinical diagnosis of emphysema. Many but not all patients with emphysema will demonstrate an increase in the anteroposterior diameter of the chest associated with hyperresonance to percussion and a tendency to obliteration of the cardiac and hepatic dullness. At one time such findings were thought to be of great aid in the diagnosis of emphysema. It is now appreciated that similar changes in the chest wall occur in many elderly persons without emphysema. Moreover, some patients with emphysema do not exhibit this phenomenon. It would appear that the barrel-chest phenomenon is related to aging changes in the skeleton. For some reason it tends to occur prematurely in patients with emphysema.

UNUSUAL FORMS OF EMPHYSEMA[1]

DAVID V. BATES

Introduction

It may sound frivolous to talk about unusual forms of a disease we cannot define, but I do not believe this is a useless pastime. It seems to me that the problems raised by difficult cases allow us to see how far we are progressing in our general understanding of the condition. If you go on looking solely at "classical" advanced emphysema, you may convince yourself you know something about it.

I would like to start off by talking about emphysema in women, which I think may be a discrete and distinct problem; it is at any rate a very interesting one. We have been concentrating on trying to find established emphysema in women who have had minimal bronchitis, and have normal bronchograms, to see if the disease is distinguished in any way from the fully developed picture in men.

One such patient was a 49-year-old lady who lives in one of the northernmost points of northern Ontario. This region has no atmospheric pollution and the patient has smoked cigarettes only on rare occasions. She came down to Montreal because she had been becoming progressively disabled with dyspnea. Her history was as follows: She had no asthma, no respiratory disease of any kind, had had no severe measles in childhood and no whooping cough that she could remember. I should add at this point that she was a very intelligent woman working as secretary to an Industrial Compensation Panel.

The patient regularly played golf, and in 1954 she noticed that she was beginning to get a little dyspneic during this exercise, which she took three times a week. In 1955, she sought professional advice about this, and on the basis of a normal roentgenogram and an absence of physical signs she was told that the trouble was nervous. Her dyspnea steadily progressed, however, and by 1957, when we saw her, she could just walk on the flat at about a mile and a half an hour. Anything more than this was too much for her. She was quite sure that she had never coughed up a blob of sputum, although during the previous winter, which was in 1956, she had had an irritative cough, and her husband commented that she was coughing a little. However, this was totally unproductive of sputum.

At the time we saw her the severity of her dyspnea on exercise was obvious, but physical examination revealed only some diminution in breath sounds over both lung fields and a little prolongation of expiration. There were no added sounds. The cardiovascular system was normal, and there was no evidence of right ventricular failure.

The function test results are shown in table 1 (*Case 1*) and show a reduction in vital capacity, a functional residual capacity a liter more than predicted, severe gas mixing inequality, and an indirect maximal breathing capacity of 12 liters per minute. The maximal midexpiratory flow rate was also extremely low, being less than one-tenth of the predicted figure. It may also be noted that the pulmonary diffusing capacity on the steady state method was well down and was grossly low, particularly on exercise. The arterial puncture showed that the patient was a little unsaturated, with slight carbon dioxide retention, but we wondered whether she held her breath as the arterial sample was withdrawn; that might possibly have influenced these findings a little.

Now by an odd coincidence this lady had had a chest roentgenogram every year since 1940, and that is what makes her unique in my experience, since her symptoms started in 1954; but she had had roentgenograms yearly before that. When we obtained these films and reviewed them we found that they were normal up to 1946, but in that year we could see that in the upper zones on both sides there was a diffuse infiltrative process. This corresponded with no illness as far as she knew and no respiratory infection. This was evident also in the 1948 film, and it had cleared completely by 1950. Then there was the steady development of loss of structure in the same zone so that the 1957 film showed established emphysema affecting predominantly those areas which had been involved in the infiltration. These changes are illustrated in figures 101 and 102. The predominantly upper lobe distribution of the emphysema was confirmed by the full chest tomogram which shows an absence of vascularity in this region. This evidence of disappearance of pulmonary vasculature is, in my opinion, the single roentgenographic sign of real value in emphysema, and we will report on this aspect of the disease at the American Roentgen Ray Society in Washington in September.

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TABLE 1

FUNCTION TEST DATA ON FOUR PATIENTS DISCUSSED

	Case 1 G. L. ♀ 49 Years	Case 2 M. L. ♂ 26 Years	Case 3 T. F. ♂ 54 years	Case 4 T. S. ♂ 24 Years	
				Pretreatment	Post-treatment
Height—inches	66	66	67	75	75
Weight—lbs.	117	126	125	132	147
Vital capacity	0.68 (3.5)	2.20 (4.7)	2.3 (3.5)	2.6	5.4 (6.0)
Functional residual capacity	4.10 (3.2)	2.34 (3.4)	4.5 (3.1)	3.2	4.4 (4.7)
Mixing efficiency %	16 (50+)	31 (60+)	48 (50+)	15	68 (60+)
Expiratory flow rate[*], L./min	12.0 (85)	72.0 (156)	52 (95)	28	176 (175)
Maximal midexpiratory flow rate, L./sec	0.25 (2.9)	2.52 (4.7)	0.98 (3.7)	0.40	5.6 (4.7)
Resting Dco mlCO/min/mm Hg	4.7 (12+)	11.0 (12+)	9.8 (12+)	10.1	25.6 (12+)
Resting O_2Hb saturation %	89	98	—	91	98
Resting pCO_2 mm Hg	58	44	—	—	42
Resting pH	7.27	7.37	—	—	7.42
Exercise rate	1 m.p.h. flat	3 m.p.h. flat	3 m.p.h. slope—20%	—	2½ m.p.h. flat
Exercise Dco mlCO/min/mm Hg	8.6 (23.0)	22.7 (36.4)	18.7 (27±3.2)	—	36.7 (36.4).
Diagnosis	Emphysema following pulmonary infiltration	Unilateral emphysema	Symptomless emphysema (old "normal")	Reversible bronchospasm	

Predicted values are shown in parentheses after the actual figure. Functional residual capacity and mixing efficiency measured by closed circuit helium technique (1). Maximal midexpiratory flow rate measured with spirometer and kymograph by technique of Leuallen and Fowler (2). Resting diffusing capacity measured by end tidal technique (3). Oxygen saturation of arterial blood measured with Beckman spectrophotometer, pH and pCO_2 measured by Astrup technique. Exercise was on a motor-driven treadmill, and the exercise Dco was calculated using the measured arterial pCO_2 in *Cases 1 2*, and *4*.

Here was a lady presenting with "classical" emphysema in which we fortuitously learned that she had had a diffuse process present in the lung for three years not accompanied by symptoms, and this was followed by the development of emphysema in the same areas. We can speculate endlessly, of course, on what this lesion was and, after reading McLean's papers, I wondered if it could have been a silent bronchiolitis.[2] It is possible, of course, that it was sarcoidosis, although there is no supporting evidence for this.

This patient illustrates the fact that, when an unusual case of emphysema is seen, the essential information needed may be totally missing. This patient is not unique, as far as the presentation of her disease is concerned. I studied a similar situation in a lady of fifty who came from Tunbridge Wells in England with precisely the same presentation. Both of these patients had one thing in common, which you will find is almost a hallmark of emphysema in women without bronchitis, and that is that they had both been

[2] This patient died on October 26, 1958. At autopsy she had marked bilateral bullous emphysema of both upper lobes with relative sparing of the upper portions of the lower lobes and completely normal lung in the bases of both lower lobes. There was no evidence of the nature of the infiltrative process which had been seen in the upper lobes in 1946. There was no lymph node enlargement, and the autopsy diagnosis was pulmonary emphysema and right ventricular failure.

Case 1

FIG. 101*A* and *B*. Postero-anterior roentgenogram and tomogram obtained in 1957. Note loss of vascularity, particularly in upper lobes of each lung.

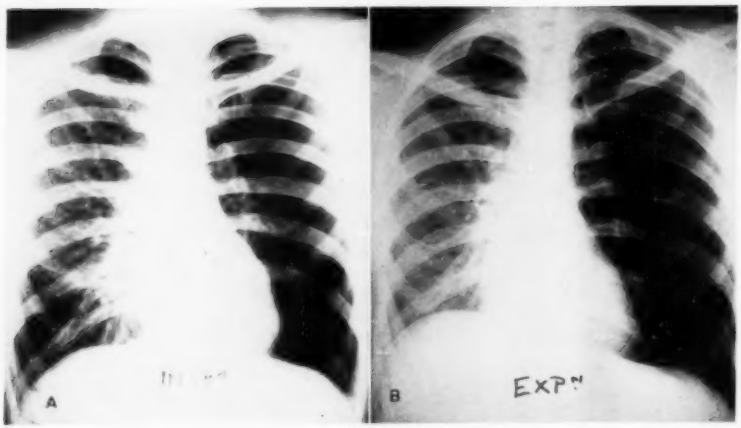
referred to psychiatrists before they had had their pulmonary function studies. The patient from England had a roentgenogram identical to the one I have shown you here, with involvement of the upper lobes predominantly, and it is of interest that she has been followed by Dr. Marshall in London for the three years since I first saw her in 1955. Dr. Marshall found that in the winter of 1956 she had had a first attack of typical chronic bronchitis, and by 1957, which was two years after we had studied her, the clinical picture was typical of emphysema and established chronic bronchitis of the customary English pattern. But it happened that we had documented the fully developed hallmarks of emphysema two years before that initial attack of chronic bronchitis took place.

The next problem, I think, raises acute issues for the pathologists, and they have studiously avoided all mention of it—a great tribute to their shrewdness. This is the problem of the purely unilateral emphysema. This condition is well documented, and I will discuss a recently studied example of the syndrome in a man of twenty-six years, completely symptomless, whose abnormal roentgenogram was picked up on routine filming. He had never had any episode of respiratory infection and had no cough. The films of this man may be seen in figures 103 and 104, and the function tests in table 1 (*Case 2*). There are about fourteen well-documented cases in the literature, and I want to emphasize some points which patients with this disease generally have in common. First, there is a normal appearance on bronchoscopy, but the bronchograms show very characteristic changes of bronchiolectasis. Indeed, they are very reminiscent of the type of bronchogram which Galbraith and Simon showed occurred in chronic bronchitis. Second, although, as you see from the angiogram, one might expect that there was some hypoplasia of the pulmonary artery, this has often been found to be missing in these cases, and there is very little evidence that the arterial lesion is in any sense primary. Nobody has yet explained why the bronchogram should be so abnormal if the arterial lesion were to be the only primary change.

Now the point to make about unilateral em-

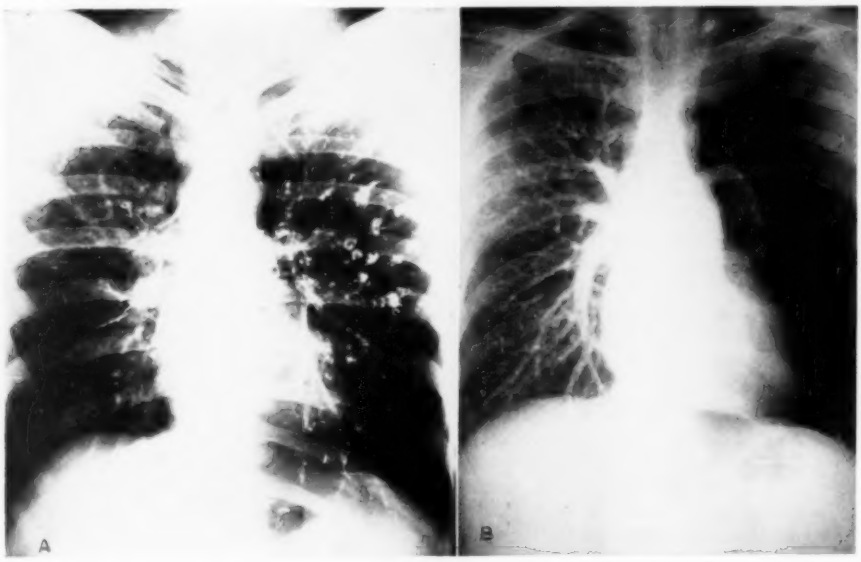
Case 1

FIG. 102. Views of upper right intercostal spaces of roentgenograms: (*A*) in 1941; (*B*) in 1946, on which film a diffuse infiltration was visible although the patient was symptomless; (*C*) in 1957, when fully developed emphysema was considered to be present.



Case 2

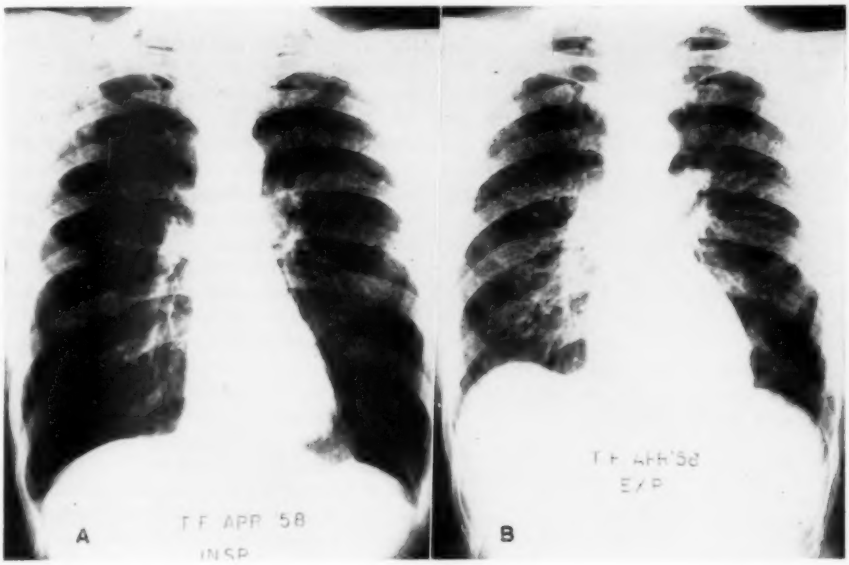
FIG. 103.*A* and *B*. Inspiration and expiration films with unilateral emphysema of "classical" type.



Case 2

FIG. 104.*A* and *B*. Unilateral emphysema showing (*A*) bronchogram and (*B*) angiopneumogram. Note the pools of radiopaque material at the end of the bronchial tree and the fact that almost all perfusion is taking place through the normal right lung. *See* text for discussion.

physema—and I was very pleased to have the opportunity to talk to Dr. McLean on this point—is that it is true emphysema as far as we can define that condition at the moment. It has every hallmark of emphysema, and the functional situation illustrates the fact that, if you are lucky enough to have a normal lung, you don't bother to use the emphysematous one; that is what these people in fact are doing. On the evidence, I think this must be accepted as "normal"



Case 3

FIG. 105.*A* and *B*. Inspiration and expiration films of *Case 3*. These were considered to be within normal limits, and the tomograms showed only slight possible loss of vascularity at the left base, but an otherwise normal vascular pattern.

emphysema within the terms of any definition we can reasonably make of that condition. These cases need to be kept very much in mind when generalizations are being made about the etiology of emphysema.

The next patient raises a problem of a totally different sort. At the age of fifty-four he volunteered as an old normal subject for studies on the pulmonary diffusing capacity.

He had a detailed history and clinical examination, and as a hospital employee had had an annual chest roentgenogram for several years. Apart from the fact that he said he had lost 14 pounds in weight in the past year, he complained of nothing. He smoked rather less than ten cigarettes a day and, when questioned directly about cough, he said that occasionally in the winter he had a blob of sputum but he has lost no time from work because of chest disease, and he did not regard his cough as a symptom. He had noticed no dyspnea. The first pulmonary function test done on this man was the exercise diffusing capacity, and we found that that was significantly lower than predicted. He was then referred for the resting function tests and, as you will see from table 1 (*Case 3*), he was found to be abnormal right across the board, all the values being altered in the direction of emphysema.

This man's expiration and inspiration films, which were considered normal, are shown in figure 105. The tomograms rather suggested a loss of vascularity in the left lower lobe but were otherwise normal. Now this raises problems of classification. Is this emphysema? It certainly isn't chronic bronchitis, as he had no sputum and he would probably not be included as a chronic bronchitic in any survey of a population designed to pick up that condition. He had every hallmark of emphysema to a mild degree. I think that this is emphysema, and I think Dr. McLean would find changes in these lungs if he had the opportunity of looking at them. In fact, I think this man, from a functional point of view, represents the men over the age of fifty who are not known to have had any respiratory symptoms, in whom Dr. McLean finds pathologic changes which are the precursors of established and severe emphysema. I think we are faced with the fact that this type of abnormality is beyond the reach of clinical or roentgenographic diagnosis and, indeed, I suggest that the maximal midexpiratory flow rate is probably the simplest way to define normality in men over fifty. The implications of this

need facing, because we will presumably go on having successions of communications in the literature on old normal subjects in which the authors say that the changes are solely attributable to age. Might I put in a special plea that women be used as control subjects in these investigations, since there is evidence that they are much less likely to suffer from this type of early emphysema.

So far I have shown you 3 patients, the first an unusual case of emphysema, the second a unilateral emphysema, and the third showing very early changes which nevertheless indicate emphysema to me. All of these people have, I think, the type of change broadly classifiable as emphysema. My last patient does not have emphysema, but I thought he probably had.

This was a 24-year-old man who had been lumbering in North Quebec when he began to get somewhat dyspneic. He had had allergic rhinitis in childhood, and this had been a constant bother to him; but it got better some four years ago and had troubled him very little since then. He had had no episodes of spasmodic asthma in the past. He said that he was just getting steadily more dyspneic, and on physical examination in June, 1957, the signs were a generalized expiratory wheeze, not very marked, in the upper zones of both lungs, and remarkably absent breath sounds of both bases. The roentgenogram at this stage was not very remarkable, but in comparison with a later film was considered to show areas of diffuse atelectasis at the bases. The function tests which are shown in table 1 (*Case 4*) show very extreme abnormality on the first occasion except for the functional residual capacity, which was not increased. It may be noted that the resting diffusing capacity was low in this man and, since in the majority of patients with asthma it is not much lowered, I wondered if he had some irreversible changes. At the time of these tests he had had all bronchodilators in generous amounts except steroids. He was consequently put on these.

I agree absolutely with Dr. Lowell, who made this point yesterday, that this is the final test of the reversibility of bronchospasm, and you will see in table 1 the reversal of the previous situation that occurred with this treatment. The maximal breathing capacity rose from 28 liters per minute to 176 liters per minute, and the mixing efficiency from 15 to 68 per cent. Presumably, the low diffusing capacity figure in this case was initially attributable to a greatly diminished surface area that he was ventilating. I may remark that, since I am on record as saying that the diffusing capacity will usually distinguish asthma from emphysema, this patient represents one of the two exceptions to this generalization which I have encountered in a study of about 110 patients with the two conditions. We know that this man did not have emphysema since the whole situation was fully reversible. This case is presented as a cautionary tale against the use of physiologic data to diagnose an irreversible condition at the present state of our knowledge. I am sure we will be in a position later to make this differentiation with absolute certainty, but at the moment we are in a position of having just a few pointers toward such a separation.

I have tried to illustrate several unusual aspects of the whole spectrum of emphysema, which I suggest to you is vastly more complicated than you would guess by looking at endless numbers of old men who have cough and fully developed changes. If I have served to illustrate to some people the oddities that crop up when it is possible to study these patients thoroughly—oddities which require and will ultimately receive explanation—then at least I feel that I have served my purpose.

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FAMILIAL EMPHYSEMA[1]

ALLAN HURST

The etiologic basis for diffuse obstructive pulmonary emphysema has been the subject of considerable discussion since the classic description of this disease by Laennec (1). In the literature on the subject in the nineteenth century, reference was made to an hereditary or familial predisposition. Two families were recently observed in whom emphysema was the major disabling problem and in whom the question of familial predisposition arose.

M family—three brothers

H. M., age fifty-seven. Died of silicosis, cor pulmonale, severe pulmonary emphysema.

A. M., age fifty-one. Died of bilateral severe bullous emphysema, and congestive heart failure. Gastroenterostomy had been done for severe unremitting ulcer pain for five years.

C. M., age fifty-one. Severe bilateral diffuse obstructive pulmonary emphysema with cough and expectoration. History of moderate cigarette smoking. Marked weight loss. Repeated bouts of respiratory acidosis with psychotic-like episodes, ending in suicide. There is a first cousin of the same age with severe dyspnea, but there are no available data.

B family[2]*—five brothers*

C. B., age fifty-three. Died in 1953 of pulmonary emphysema, cor pulmonale, and congestive heart failure. The onset was in 1944, and it was noted that the patient had had asthmatic attacks in 1947 and 1948. An incidental finding was duodenal ulcer.

J. B., age fifty-two. Died in 1951; was first seen in 1940 with rather severe asthma and emphysema. Patient had typical downhill course with congestive heart failure.

D. B., age fifty. No asthma; duodenal ulcer; severe pulmonary emphysema with disability.

N. B., age fifty-three. No history of pneumonia, asthma, or bronchitis. With each respiratory infection, he develops acute anoxic picture and requires hospitalization. He has smoked a pack of cigarettes daily for twenty years. Studies in the cardiopulmonary laboratory show evidence of severe emphysema.

E. B., age forty-seven. Slight but increasing dyspnea on effort, such as climbing a grade. He has had a mild cough, has no asthma, and is a moderate smoker. Through the cooperation of the University of Iowa Medical School, studies were done. The findings were those of an increase in residual volume, uneven distribution, large physiologic dead space, and diffusion in the lower limits of normal—all consistent with early pulmonary emphysema.

Three sisters, one of whom was a fraternal twin of *D. B.*, are all well.

In attempting even a casual review of the literature with reference to familial predisposition, one is struck by the large number of publications by the English. Whether because of climatic factors or otherwise, chronic bronchitis is an important disease there and, as Fletcher (2) pointed out, "this really means emphysema." Accordingly, most treatises on chronic bronchitis were scanned, hoping to find references to hereditary factors. Of these, Badham's (3) is the first to include the term "bronchitis" and, written in 1808, shows great understanding of basic distortion of physiology.

Neither Laennec (1) nor Stokes (4) mentions familial factors but Louis (5), quoting his own observations as well as those of Jackson, states that the disease is often hereditary. He noted that of fourteen persons whose dyspnea was traced to early youth, fourteen had asthmatic parents; while of fourteen attacked later in life, two only were the offspring of parents who died of the same disease.

Dobell (6) wrote:

> These statistics, therefore, which we are supposed to have in evidence of the hereditary nature of emphysema, must be taken with considerable caution. . . . If then, the tendency to bronchitis and catarrh is hereditary, and if catarrh is hereditary, and if catarrh and bronchitis are common causes of emphysema, it is easy to see how naturally the mistake has arisen of concluding that emphysema itself is hereditary.

Loomis (7), in discussing primary emphysema, thought that "there exists in many persons either a hereditary or an acquired impairment of the elasticity of the lungs, which renders them more readily dilatable and more easily torn."

[1] From the Department of Medicine, University of Colorado School of Medicine, Denver 18, Colorado.

[2] Information on most of this family was supplied by the McFarland Clinic, Ames, Iowa.

Fothergill (8), in a beautifully written and most picturesque treatise, had nothing to say on hereditary factors. West (9) stated that inheritance was important and quoted Lebert as stating that 13 per cent of 108 cases showed familial patterns. He also cited Schnitzler who "records an instance of three brothers who became emphysematous at the age of 30 without obvious cause" and Hertz who cites another instance of 4 members of the same family having the disease. Gee (10), speaking of chronic bronchitis, believed that it was often hereditary. More recently, Oswald and associates (11) stated:

> The high incidence of bronchitis among the relations of bronchitic patients, the figure being three times as great as for controls, suggests a hereditary predisposition. This is probably the correct interpretation, since social and economic factors were eliminated as far as possible by making every effort, short of visiting their homes, to obtain comparable groups of patients and controls. Also, the part played by cross-infection within the families, although virtually indeterminable, is unlikely to be important and because of the late onset of bronchitis in most of the patients.

Ogilvie and Newell (12), however, state that:

> The definite association with bronchitis in the family cannot be taken as certainly due to heredity, as it might be due to cross infection within the family circle, as pointed out by Stuart-Harris (1954). But the evidence of this is, so far, suggestive only, and the fact that no evidence of the existence of 'bronchitic households' was found (see page 51) is perhaps rather against it as more than a partial explanation.

Sorsby (13) quotes Roessle (14) as his authority for the familial occurrence of idiopathic emphysema. Roessle reports 31 cases, but notes a high correlation of this disease with left ventricular hypertrophy. No explanation is attempted. Wenk (15) is of the opinion that the occurrence of several cases of emphysema in one family suggests an hereditary predisposition.

A number of physicians were asked to comment on their experience with familial emphysema. C. M. Fletcher noted that chronic bronchitis has a tendency to occur in families. A number of men had seen several cases in one family. Several expressed the opinion that genetic factors might play a role in determining the quality of pulmonary elastic tissue.

At present, one may conclude that there may be a familial tendency in emphysema, but whether the disease develops may depend upon sex, occupation, smoking habits, and exposure to noxious inhalants.

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THE RELATIONSHIP OF ALLERGY TO EMPHYSEMA[1]

FRANCIS C. LOWELL

In what follows, I am using the word "emphysema" to mean a progressive and relatively irreversible diffuse obstructive disease appearing alone most frequently in males over the age of forty. The similarity between this disease and asthma, traditionally an allergic disease, is perhaps a reason for suspecting a role for allergy in emphysema.

Is it possible that emphysema lies at one extreme of a continuous spectrum which has asthma at the other extreme? Thus, one might proceed from seasonal asthma (clearly an allergic disease) through perennial forms wherein allergy seems to play a less dominant role, to "intrinsic" or "idiopathic" forms in which no allergic mechanism is discernible, and finally to emphysema. Viewed in this way, emphysema might be placed within the family of allergic diseases. If, on the other hand, a clear line can be drawn between asthma and emphysema, we might no longer be tempted to postulate for emphysema a pathogenesis similar to that for asthma.

I am sure that I am not alone in believing that this separation can be made with a fair degree of certainty in all but a few cases. Eleven points of difference are listed in table 1. In addition to these eleven points, there appears to be a quantitative difference in the diffusing capacity and a difference as well in the location of the obstructive defect.

It is very probable that many instances of emphysema of the type under consideration have been unwittingly designated as bronchial asthma, thus creating serious difficulties in the classification and understanding of asthma. Classifications of asthma, of which there are a number, make room for a form variously referred to as "intrinsic," "idiopathic," or "non-allergic"; a second category, "infectious," is also often included. Among these patients are many who are so classified only because they wheeze. This sign tends to be equated with asthma—a deplorable tendency which dignifies a simple and inconstant physical finding with the accoutrements of a complex and as yet poorly understood pathologic process—and further, robs the word "asthma" of useful meaning.

In the New England area, at least, patients with the characteristics enumerated on the right hand side of table 1, with very few exceptions, give a history of heavy smoking and we, as well as some others, are now convinced that smoking is the predominant cause of the disease (1–5). Furthermore, in a recent survey of employees in a modern clean factory (6), we found obstructive abnormalities of minor or moderate degree among patients forty years of age or older to be significantly more common among heavy smokers than among light- and nonsmokers. The P-value for the difference in the two groups was less than 0.01.

The absence of wheezing in many—but by no means all—instances of emphysema, despite striking obstruction to airflow, suggests flow of air through minute passages where turbulence would not occur. Tobacco smoke, composed as it is of minute particles, could easily reach the most distal ramifications of the airway, the probable site of obstruction. The fact that wheezing is an outstanding feature of asthma places the lesion in the larger airways, at points where the relatively much larger air-borne allergens—pollens, mold spores, and house dust—would tend to impinge.

A relationship between smoking and emphysema is so firmly fixed in my own mind that it has become quite impossible for me to consider the etiology of emphysema of the type described at the outset in terms other than lung damage caused by inhalation of noxious smokes, fine dusts, and smogs. As a result, I shall limit further discussion of the role of allergy in emphysema to the possibility that the disease is the consequence of some type of allergic reaction to these substances, among which tobacco smoke seems to be far and away the most important. If this is too narrow a point of view, I can only say that the program committee selected the wrong person to talk under this title.

What do we know about allergy to tobacco smoke? Actually very little. Most of the work has been done by skin testing with extracts of cured

[1] From the Boston University School of Medicine, Boston 18, Massachusetts.

TABLE 1

DIFFERENCES BETWEEN BRONCHIAL ASTHMA AND "IDIOPATHIC" OBSTRUCTIVE PULMONARY EMPHYSEMA

Bronchial Asthma	"Idiopathic" Obstructive Pulmonary Emphysema
Makes its first appearance predominantly in children and young adults.	Onset usually after the age of forty years.
Tends to run in families, including members who have or who have had asthma, hay fever, infantile eczema, and a tendency to brief attacks of urticaria.	No familial tendency established.
Incidence higher in boys than in girls; in women than in men.	Occurs predominantly in males.
May be present for many years without permanent pulmonary dysfunction of clinical significance.	Irreversible pulmonary dysfunction of marked degree usually develops within a few years (two to five) after patient *first* notes dyspnea on exertion.
Many patients with asthma do not smoke, giving as their reason for not so doing that smoke is irritating to the airway.	A history of heavy cigarette smoking is the rule, in the New England area at least.
Patients with an asthmatic attack have orthopnea and dyspnea at rest.	Patients with uncomplicated emphysema usually do not have dyspnea *at rest* and can usually lie flat without discomfort.
During an attack, loud and distinct musical rales and rhonchi are heard on auscultation.	Although similar auscultatory signs may be present, they are often absent, despite the presence of a striking obstructive abnormality.
As a rule, striking skin reactions of the "immediate" type are elicited by the intracutaneous injection of suitably prepared extracts of common aero-allergens and, less frequently, certain foods.	Skin reactivity to allergenic extracts is usually absent or minimal.
Blood eosinophilia of more than 300 cells per cu. mm. is the rule.	Eosinophilia is usually absent.
The process is "reversible." Exacerbations or even persisting asthma of severe degree characteristically respond to steroid therapy with a marked improvement in pulmonary function to, or close to, normal.	The process is "irreversible." Even after the most intensive therapeutic regimen, severe functional abnormality remains.
Cor pulmonale is an uncommon complication.	Cor pulmonale is a common complication.

tobacco leaf—not with extracts of tobacco smoke, which, by the way, tend to be irritating. In the course of reviewing the published work on allergy to tobacco not so long ago (7), it appeared that extracts of tobacco *leaf* were indeed capable of inducing allergic manifestations other than contact dermatitis, although reasonably complete reports of such instances could be counted on the fingers of one hand. There is also a more recent review (8). I am aware of no well-documented evidence bearing on pulmonary reactions to tobacco smoke on an allergic basis, although these may indeed occur among some asthmatic persons, who state that smoke aggravates their symptoms. On the other hand, such instances may merely be a manifestation of their susceptibility to any air-borne irritant. There is no good evidence, to my knowledge, that these instances constitute allergic responses in the immunologic sense. An allergic response in the lung is, therefore, only a vague entity among our best indicators, namely asthmatic subjects, and it does not seem reasonable to postulate any such response in emphysema.

I shall confine myself to only one more point. A role for the tuberculin type of allergic response to tobacco smoke is at least in harmony with what we know about emphysema. The tuberculin type of allergic response does not seem to confine itself to certain predisposed persons in the population as does the atopic type, and the tuberculin type of allergic response can unquestionably lead to a destructive and irreversible form of inflammatory reaction. Such a reaction could produce the widespread damage and destruction seen in the emphysematous lung. So far so good; but I know of no evidence for this, and it must remain a matter for mere speculation.

To say that an allergic response is not demonstrably involved in the pathogenesis of emphysema is not to say that allergic responses do not accompany emphysema. Patients with this disease tend to have recurring pulmonary infections, and the complex inflammatory events associated with infections unquestionably include allergic responses to components of invading organisms. To what extent these processes contribute to the progression of the disease is unknown, but I personally regard them as secondary to injury by inhaled irritants and not as the primary lesion.

As I see it then, emphysema is quite distinct from asthma in its pathogenesis, and I am unable to find evidence that an allergic response of any type is primarily involved.

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General Discussion

Dr. Coates: I would like to make several comments which lend some documentation to Dr. Lowell's impression regarding smoking and emphysema. Dr. Geoffrey Brinkman and I have been

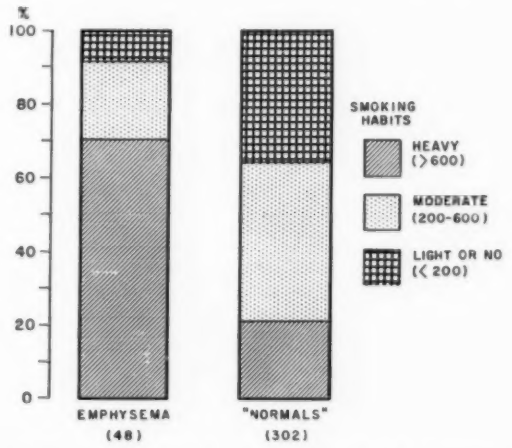

Fig. 106. Cigarette smoking in persons more than forty years of age.

following a group of persons over forty years of age who live in Detroit and whom we call "normal" because they are well and working and have no symptoms. We have compared the incidence of heavy smoking in the "normal" group with the incidence in a group with confirmed emphysema, that is, in persons who fit the clinical and physiologic criteria we use to identify obstructive emphysema.

Smoking was graded by the number of cigarettes per day times the number of years the person had smoked, so that a figure of 600 represents 30 cigarettes daily for 20 years, or a combination thereof. Light smokers were defined as those who had smoked 20 or less cigarettes daily for ten years at the most.

That the difference between these two groups of smokers is striking is shown in figure 106. About 70 per cent of the emphysema group were heavy smokers, whereas only 22 per cent of the normal group were heavy smokers. The "normal" group, incidentally, consisted of approximately equal numbers of executives and men who worked in factories where they were potentially exposed to dust or fumes.

The other point I would like to make refers to the relationship of cigarette smoking to "airway obstruction," as measured by the three-second vital capacity and the maximal midexpiratory flow rate, the latter being the more reliable test in our hands. The proportion of heavy smokers who had reduced screening tests for airway obstruction was compared with the proportion of light smokers who had airway obstruction. Using rather arbitrary average normal levels, the difference between the two groups was statistically significant.

We should concern ourselves not only with the possible relationship of smoking to lung cancer, but also with its relationship to emphysema. The points mentioned indicate, I believe, that more work along this line is needed. A final point is that we urgently need to know whether simple screening tests for airway obstruction will detect cases of early emphysema.

CHRONIC BRONCHITIS AS AN ETIOLOGIC FACTOR IN OBSTRUCTIVE EMPHYSEMA[1, 2]

Preliminary Report

EDWARD A. GAENSLER[3] AND INGA LINDGREN

INTRODUCTION

We regret that Dr. Wright was unable to address this Conference on the subject of "air pollution." We have no knowledge concerning this topic except that, wherever modern man lives in great numbers, the surrounding air, much as the lakes and streams, is quite polluted. We do not know whether we should be alarmed that 2.1 million tons of soot or 24 million tons of carbon monoxide are deposited annually over Great Britain (1) and that automobiles in Los Angeles County discharge more sulfur, in the form of sulfur dioxide, than the entire commercial sulfur production of the world (2).

When we were asked to prepare a paper on chronic bronchitis it occurred to us that, thanks largely to our British colleagues, this disease during the past ten years has changed from a layman's diagnosis of "bronical trouble" to a quite respectable and much discussed disease entity. This interest may have been stimulated by air pollution accidents such as the Meuse disaster, the Donora Valley incident, and the 1952 London smoke fogs (3, 4). In each case fatalities were concentrated among those with chronic respiratory disease. The fairly obvious relationship between smog and aggravation of productive cough has aroused many communities (5). Cigarette smoking has been incriminated during recent years, not only in regard to bronchogenic carcinoma, but also in a variety of other diseases, particularly chronic bronchitis. Finally, a steadily decreasing mortality from some respiratory diseases, particularly tuberculosis and lobar pneumonia, has brought into sharper focus mortality rates of respiratory diseases with steady or increasing incidence, especially carcinoma and chronic bronchitis (6).

The index to abstracts in the AMERICAN REVIEW contains three references to "Bronchitis, chronic" during the five-year period from 1949 to 1953. During the next five years, from 1954 to 1958, 38 papers are listed under the same heading. Evidently this disease has not created equal excitement in the United States: not a single article on this subject has appeared in the AMERICAN REVIEW itself during this ten-year period. In Great Britain there appears to be a sincere concern by many about this "English disease" and the "British national institution of the cough bottle." We are told that 20,000 to 30,000 people die there each year of chronic bronchitis; that deaths due to this disease exceed the mortality from tuberculosis, bronchopneumonia, and bronchogenic carcinoma; that among all causes of death it is surpassed only by heart disease, cerebral vascular accidents, and carcinoma; and that it causes loss of 16.5 million working days per year (7, 8). Furthermore, chronic bronchitis is responsible for more than 50 per cent of all military medical discharges (9) and is the cause of 15 per cent of all civil service retirements due to ill health (8). The concern of general practitioners appears well justified in that 8 to 11 per cent of all medical visits are because of chronic bronchitis (1, 8). The peculiarly British character of this disease appears to be supported by surveys of the World Health Organization which indicate that death rates from chronic bronchitis per 100,000 are 65 for England and Wales, 47 for Northern Ireland, and 43 for Scotland, while these rates are only from 2 to 4 for Canada, Finland, Sweden, and the U. S. A. (10).

It must have occurred to others that the climatic, social, and industrial conditions in southern New England are not unlike those prevalent

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[2] This study was supported, in part, by research grants from the National Heart Institute, U. S. Public Health Service (H-1773), and from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association.

[3] Edward Livingston Trudeau Fellow.

TABLE 1

PULMONARY FUNCTIONAL CRITERIA FOR INDEXING UNDER "EMPHYSEMA"

Maximal breathing capacity	less than 80% of predicted
Air velocity index	less than 0.8
Per cent of vital capacity in first second	less than 70%
Residual volume	more than 125% of predicted
Pulmonary mixing index	more than 1.5% N_2
Bronchodilator aerosol	less than 20% increase of maximal breathing capacity

in Great Britain. In both areas the weather is generally inclement; because of lack of water power a great deal of coal and oil is burned throughout the year; automobile traffic and heavy industry are moderately concentrated; and the populations are relatively stable. WHO statistics, quoted above, suggest that "chronic bronchitis" is not a popular death certificate diagnosis in the U. S. A. An investigation of this disease must therefore come from a different direction. Most physicians in Great Britain have a very definite idea concerning diagnostic aspects of chronic bronchitis, but their ideas regarding chronic obstructive emphysema often are rather vague. The authors like to believe they have fairly well-defined impressions concerning the pathophysiologic and diagnostic aspects of chronic obstructive emphysema, but their ideas concerning chronic bronchitis are rather vague. An attempt was made therefore to search for the incidence of chronic bronchitis, as defined by the British, in a group of patients with chronic obstructive emphysema as defined by us.

Until this study we had certain preconceived notions concerning our past experience with emphysema and bronchitis. We thought: (*1*) that chronic obstructive emphysema probably is ten to twenty times more common in men than in women; (*2*) that the large majority of patients have "dry emphysema," that is, without cough and expectoration except during intercurrent infections; and (*3*) that nearly all of our patients are, or were until recently, heavy cigarette smokers.

DEFINITIONS AND METHODS

Definition of obstructive emphysema: Certain basic screening and pulmonary function tests have been performed on nearly all patients in our laboratories since 1948 except that timed vital capacities were not obtained until 1949 (11) and breath-holding tests were abandoned in 1950 (12). In general, a cross-index card was prepared under the subject of "emphysema" every time all of the abnormalities indicated in table 1 were observed. These included abnormally low maximal breathing and one-second timed vital capacities and air velocity index, and abnormally high residual volume and pulmonary mixing index. Patients with these findings but with an improvement of maximal breathing capacity and timed vital capacity of more than 20 per cent after bronchodilator aerosol usually were indexed under "bronchial asthma." The percentage of total lung capacity (TLC) occupied by residual volume (RV/TLC ratio) is not listed in table 1. Although a report had just been published on a large series of emphysema patients who were selected on the basis of a RV/TLC ratio of more than 35 per cent (13), we omitted this criterion because many of our patients had a high ratio because of a decrease of total lung capacity rather than an increase of residual volume. The total vital capacity was not included because it bore no relationship to obstructive emphysema.

Obviously, the criteria of table 1, by definition, excluded all patients with early or minimal obstructive emphysema. Indeed, we believe that now, ten years later, we are still unable to diagnose this disease in its earliest form.

Definition of "chronic bronchitis": A search for a definition of chronic bronchitis leaves one quite bewildered. All too frequently "asthma" or "spasmodic breathlessness" appear among description of symptoms (14). Some studies of bronchitics included those with periodic and seasonal breathlessness relieved by sympathomimetics. In one of the largest series, 70.6 per cent of patients were regarded as being subject to bronchospasm (15). Indeed, some believe that chronic bronchitis is a mild form of asthma (16).

"Dyspnea" is another ever-recurring term in the various definitions. Usually it is considered a late symptom, but Oswald, for example, after interviewing 1,000 patients with chronic bronchitis, finds that 87.7 per cent ". . . had either spasmodic or constant breathlessness or both." He goes on to say: "A large number of these patients, probably the great majority, would not have been regarded as having chronic bronchitis if they had not been breathless" (15). Emphysema is thought to accompany or to be an end result of chronic bronchitis, but no studies have been made to ascertain which is the cart and which the horse. Worse, cor pulmonale is often mentioned in definitions of bronchitis, and has been considered an index of the incidence and severity of chronic bronchitis (17).

The severity and chronicity of the major symptoms, cough and sputum, also have not been well defined. Some consider a patient to have chronic bronchitis if he admits to productive cough lasting more than two weeks for two winters in suc-

TABLE 2

CLASSIFICATION OF PATIENTS FOR THIS STUDY

I. *"Chronic Bronchitis with Emphysema"*
   (a) Cough and expectoration *preceding* dyspnea by 3 years or more
   (b) Worse in winter, in morning, and with fog, dust, and smoke
   (c) Usually: "bronchitis," "smoker's cough," "pneumonia," "1918 flu," "gassed in World War I"
   (d) Physical findings suggesting bronchopulmonary infection
II. *"Wet Emphysema"*
   (a) Cough and expectoration beginning months or years *after* onset of dyspnea
   (b) Usually: no cough or expectoration in summer with continuing dyspnea
   (c) Often: pneumonia, CO_2 narcosis in winter
   (d) Variable physical findings
III. *"Dry Emphysema"*
   (a) Dyspnea
   (b) No cough, sputum, no history of pulmonary infection
   (c) No physical findings suggestive of bronchopulmonary infection

cession (18). This definition would implicate most New Englanders, including the authors.

Our understanding of the essence of the British definitions of chronic bronchitis is as follows: it is a disease characterized by prolonged productive cough either of insidious onset or beginning with a major acute respiratory infection. Cough and sputum are almost invariably worse in winter, worse in the morning, and worse with changes in temperature, foggy weather, and with exposure to smoke and dusts. The disease is slowly progressive, worse after each major infection, and may lead to obstructive emphysema.

Criteria set up arbitrarily for this study are shown in table 2.

Group I ("chronic bronchitis with emphysema") includes all patients in whom chronic bronchitis may have been an etiologic factor. These patients gave a history of chronic bronchitis, as defined above, preceding the onset of dyspnea by three or more years. Most patients in this group volunteered that they had bronchitis for anywhere from ten to forty years before onset of exertional dyspnea. The beginning of bronchitis was often attributed to a bout of pneumonia, to the "1918 flu," or to "being gassed during World War I." A few characterized their symptoms as "smoker's cough" which was described as productive, chiefly in the morning, and worse during winter. Most had positive physical findings including rhonchi, loud scattered rales, and occasional wheezes.

Group II ("wet emphysema") included all patients who, at the time of examination, presented much the same picture as patients of *Group I* but differed in that cough and expectoration had come some months or years *after* the onset of dyspnea. Often the patients had no cough or sputum during the summer, although dyspnea persisted; several had been hospitalized during recent winters with bronchopneumonia and, occasionally, with acute respiratory insufficiency. It was thought reasonable that in this group repeated acute and chronic respiratory infections may have been *the result* of obstructive emphysema with its diminished tussive force, bronchiolar obstruction, and altered bronchial epithelium. Historically, chronic bronchitis did not appear to be the etiologic agent in the development of emphysema, although it is admitted that differentiation between *Groups I* and *II* was based largely on the patients' and relatives' memory.

Group III ("dry emphysema") included all patients who had dyspnea as the presenting complaint, but no cough or sputum either at the time of examination or at any time in the past. These were patients in whom infection did not appear to play any part in the development of emphysema or contribute to present complaints. The possibility that they may have "silent" bronchitis cannot be excluded. Dr. MacLean mentioned yesterday patients with early emphysema with pathologically demonstrable bronchiolitis but without symptoms. Recent reports suggest that patients with "dry emphysema" after therapeutic tracheostomy not uncommonly have long strings of viscid purulent material removed from the trachea and major bronchi by suction, although there has been no previous cough, expectoration, or positive physical findings (19).

RESULTS AND DISCUSSION

During the ten-year period from January 1, 1948, to January 1, 1958, a total of 3,422 patients were studied at the Pulmonary Division

TABLE 3

MATERIAL FOR STUDY AND INCIDENCE OF EMPHYSEMA

Pulmonary Function Studies 1947–1957

Total number of patients	3,422
No tuberculosis	1,889 (55.2%)
Tuberculosis, active or arrested	1,533 (44.8%)

Incidence of Emphysema

	Total Number of Patients	Number with Emphysema	Per Cent with Emphysema
Nontuberculous	1,889	555	24.4
Tuberculosis, "special preoperative" (referred)	753	459	61.0
Tuberculosis, "routine preoperative" (own patients)	780	332	42.6

TABLE 4

REASON FOR REFERRAL OF NONTUBERCULOUS PATIENTS WITH EMPHYSEMA

	Per Cent
Dyspnea	36
Dyspnea, ? bronchial asthma	14
Dyspnea, bronchogenic carcinoma (pre-surgical)	9
? Cor pulmonale	8
? Lung cysts, ? bullous emphysema	7
Dyspnea, industrial exposure	7
Dyspnea, ? bronchiectasis	5
Dyspnea, ? anesthesia risk	5
Spontaneous pneumothorax, ? emphysema	3
Dyspnea, kyphoscoliosis	2
Dyspnea, cardiac failure, ? cor pulmonale	2
Polycythemia, ? secondary	2

of the Heart Station and at the Physiology Laboratory of the Sanatorium Division (table 3). More than one-half (55.2 per cent) did not have pulmonary tuberculosis. Of the 1,889 in the nontuberculous group, 555 (29.4 per cent) had chronic obstructive emphysema by the criteria of table 1 (table 3). This is not informative concerning any kind of incidence. It merely means that 29.4 per cent of all nontuberculous patients referred because their physicians for one reason or another wished to have a more precise definition of their pulmonary function turned out to have cross-index cards filed under "Emphysema" according to criteria of table 1. Were it not for our generally known special interest in the pulmonary fibroses and granulomatoses and the "alveolar-capillary block" syndrome, the emphysema percentage undoubtedly would have been much larger.

We then had 555 patients available for analysis. Because of the brief time available, it was decided to select for analysis in alphabetical order the first 100 records which contained histories adequate for classification. Selection in this manner may not be a permissible statistical maneuver, but it seems reasonable to believe that the type of obstructive emphysema would not be different in the Andersons, Bates, or Briscoes than in the Wyatts, Youngs, or Zarits.

The first 119 records were read in order to obtain 100 with satisfactory clinical histories. Although all patients had more than adequate studies for classification according to table 1, 19 history and physical examination records were unsatisfactory. We have often been more concerned with the ailment of machines rather than with the ailments of patients, and the emphasis has been on "objective data." Of the 19 records which were discarded, there was no clinical history in 11, insufficient information in 6, and 2 histories proved illegible.

Reason for referral: An appropriate line exists in our clinical questionnaire for the reason for referral. This may be a diagnosis, a tentative diagnosis, an historical event, a roentgenographic finding, or a symptom (table 4). By far the largest number of patients, 80 per cent, had a chief complaint of dyspnea. Chronic obstructive emphysema was frequently mentioned, and studies were then requested to quantitate the severity of the disease. Bronchial asthma was mentioned or had existed previously in 14 per cent but, if the patients were included here, they were found to have largely irreversible pulmonary destruction. The most common pathologic diagnosis in association with emphysema was bronchogenic carcinoma—found in 9 per cent. Patients with proved lesions were referred preoperatively for evaluation of surgical risk. The final decision was usually made on the basis of bronchospirometric findings. The very common coincidence in our series of emphysema with bronchogenic carcinoma (as well as duodenal ulcer) again raises the question of a possible common structural or metabolic defect, or common toxic agent predisposing to all three diseases. Many patients were referred in cardiac failure, and with evidence of chronic pulmonary disease. The total number of patients with cor pulmonale was larger than indicated because this was often not recognized by the referring physician. Other patients were referred because of silicosis, byssinosis, chronic berylliosis, or other industrial diseases which had obstructive emphysema as the end result. An increasing number of general surgical patients were sent with dyspnea for evaluation of anesthesia risk and to plan postoperative care. The remaining listings shown in table 4 would have increased if the study has been enlarged.

Sex distribution: Analysis of the sex incidence of the first 100 patients revealed a much larger number of females than we believed we had seen over the years: the ratio of men to women was 3.76:1 rather than 10 or 20:1, as we had believed (table 5). It seemed though, that the mechanics

TABLE 5

SEX INCIDENCE AND "TYPE" OF EMPHYSEMA

	Per Cent
Sex Incidence	
Male	79
Female	21
Ratio 3.8:1	
"Type" of Emphysema	
I. "Chronic bronchitis and emphysema"	68
II. "Wet emphysema"	18
III. "Dry emphysema"	14

of breathing generally were worse among the men. Whenever in the past we assembled a group of patients with very far advanced emphysema, the ratio of men was much higher: in one of our series of 19 patients with very far advanced disease there were only 2 women (20), in another all 9 were men (21), and in a third group of 47 "severely disabled by obstructive disease" there were only 5 women (22). Cor pulmonale, on the other hand, appeared to be relatively more frequent among women but, since the total number of patients with cor pulmonale was small, the difference may not have been significant.

Chronic bronchitis and emphysema: Analysis of our records concerning the history and duration of cough and expectoration, according to the outline presented in table 2, disproved our notion that most of our patients have "dry emphysema" (table 5). Only 14 per cent of all patients with emphysema had no cough or sputum and no history of acute exacerbations including these complaints. Slightly more, 18 per cent, complained of productive cough, usually during the winter and usually with exacerbations, but they indicated that these complaints had begun some months or years after the onset of dyspnea. The large majority (68 per cent) gave histories which would be described by the British as entirely typical of chronic bronchitis. Their condition, with cough and expectoration growing worse over the years and preceding dyspnea by three or more years, is outlined in table 2. From our preliminary data it appears that two-thirds of patients with moderately to far advanced chronic obstructive emphysema seen in our laboratory give a history alleged to be typical of chronic bronchitis. Because of the chronologic order of the complaints, chronic bronchitis may well have been a primary etiologic factor.

Cigarette smoking, chronic bronchitis, and emphysema: The histories were analyzed in an attempt to elucidate the relationship, if any, between smoking, chronic bronchitis, and emphysema. Classification of the degree of smoking proved simple. A "smoker" was any individual who had smoked ten cigarettes or more per day for ten years or more, and a "non-smoker" was any individual who had never smoked cigarettes (table 6). There was no need for in-between categories because none of the smokers had smoked lesser amounts or for a shorter duration. There were a number of the smokers who had stopped for six months to two years before they were seen, always at the advice of their physician and always because cough, expectoration, and dyspnea had become intolerable. These were included in the "smokers" group. Unfortunately, sufficient information about smoking was not available in all of the first 100 histories. Twenty times the question concerning smoking was not asked, or merely answered by "yes" or "no." The results shown in table 6 refer to the remaining 80 patients. Of these, 69

TABLE 6

EMPHYSEMA AND CIGARETTE SMOKING

Definition

"Smoker": 10 cigarettes per day or more for 10 years or more*

"Non-smoker": No cigarettes

Smoking Histories and "Type" of Emphysema

"Type" of Emphysema	"Smokers"	"Non-Smokers"
	Per Cent	*Per Cent*
All 80 emphysema patients†	69	31
49 "chronic bronchitis and emphysema"	69	31
17 "Wet emphysema"	65	35
14 "Dry emphysema"	71	29

* Several "smokers" had stopped from a few months up to 1.5 years before they were seen by us. There were none who smoked fewer cigarettes or for a shorter time.

† Histories of 20 patients were unsatisfactory for this analysis.

per cent were smokers. Formerly, it had been our impression that nearly all of our male emphysema patients were heavy smokers. In this group, nearly one-third were non-smokers, including nearly two-thirds of all women. In this small series smoking did not appear to affect the type of emphysema: in each of categories I, II, and III, one-third were non-smokers.

In recent years physicians overseas have given a great deal of attention to the relationship between smoking and chronic bronchitis. Nearly all have found a significantly higher incidence of this disease in smokers (15, 18, 23–28) though opinion does not appear to be unanimous (8). When one considers how long it has taken and what large numbers of patients were required to establish the association of smoking with bronchogenic carcinoma—an easily established "yes or no" pathologic diagnosis—one realizes how much more difficult it will be to prove to the satisfaction of statisticians the relationship, if any, between smoking and chronic bronchitis and/or emphysema—both relatively tenuous and unsettled diagnoses.

Tuberculosis, chronic bronchitis, and emphysema: Of the 1,533 patients with pulmonary tuberculosis, 753 were called "special preoperative" (*see* table 3). These patients were referred from twenty-three other hospitals and sanatoriums because surgery was planned and they had dyspnea, known low vital and timed vital capacities, or complex bilateral problems. It is not surprising that 459 (61 per cent) had chronic obstructive emphysema as defined in table 1; they would not have been seen had they not had severe respiratory problems. No statistical significance could be attached to the incidence of emphysema in this group. The other half of the tuberculous patients, 780 in number, were labeled "routine preoperative." The incidence of chronic obstructive emphysema of 42.6 per cent in this group is both striking and significant because they were our own surgical patients who were studied routinely preoperatively regardless of their age or clinical and functional status. The inference to be drawn from these figures is that 42.6 per cent of all patients in a large municipal tuberculosis sanatorium who have pulmonary tuberculosis severe enough to require surgery, but not so severe as to consider the situation hopeless, have moderate to severe chronic obstructive emphysema.

The large incidence of chronic obstructive emphysema in patients with advanced pulmonary tuberculosis is of considerable interest. Here is a well-controlled situation in a large group of patients, all of whom have varying degrees of specific chronic bronchitis. We have never believed that overdistention of lung tissue adjacent to contracted areas necessarily led to obstructive emphysema and we deplore the term "compensatory emphysema." Three years ago, in Milwaukee, we presented results of a survey of the incidence of chronic obstructive emphysema in 200 patients with active, moderately to far advanced pulmonary tuberculosis who had not been operated upon and who had had tuberculosis for more than two years (29). Vital and timed vital capacity results of this survey are shown in figure 107. In the first column are shown 43 patients (21.5 per cent) who had a "normal" stroke volume with a vital capacity over 80 per cent of the predicted, and "normal" rate of expiratory flow with 72 per cent of vital capacity or more delivered during the first second. The second group of 68 patients (34 per cent) had the type of ventilatory defect anticipated in moderately to far advanced tuberculosis: a restriction of the stroke volume with a vital capacity of less than 80 per cent but, for this reduced volume, a normal expiratory flow rate. The third group of 33 patients was most interesting: all had stroke volume within the predicted normal, yet marked evidence of diffuse respiratory obstruction with sharply reduced timed vital capacity. Actually, the majority exhaled less than 50 per cent of vital capacity during the first second. The last group of 55 patients had a reduction of stroke volume either because of loss of lung tissue from tuberculosis, or because of emphysema, at the expense of increased residual volume. All in this group in addition showed marked obstruction.

From this superficial survey it appears that 44 per cent of all patients with moderately to far advanced pulmonary tuberculosis of at least two years' duration have a significant degree of chronic obstructive emphysema. Interestingly, this figure in 200 medical patients corresponds closely to 42.6 per cent emphysema observed in 780 patients studied routinely but in much more detail prior to surgery for tuberculosis (*see* table 3). Detailed studies of the mechanics of breathing, lung volumes, and arterial blood at

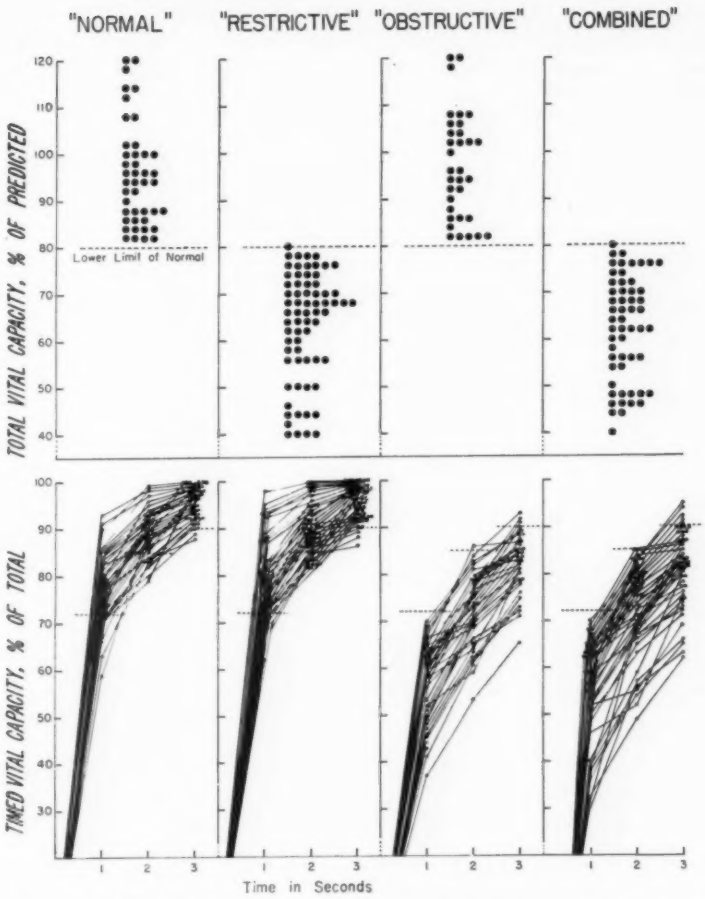

FIG. 107. A survey of 200 patients with active, moderately, or far-advanced pulmonary tuberculosi of more than two years' duration. Vital capacity (as per cent of predicted) and one-, two-, and three second timed vital capacities (as per cent of total vital capacity) are shown.

rest and during exercise on 11 patients of this group showed no physiopathologic difference, either qualitative or quantitative from the picture seen in the common or garden variety of chronic obstructive emphysema (29). Obstruction of that severity must be diffuse and hence must involve lung tissue largely unaffected by tuberculosis. This suggests that the chronic bronchitis of tuberculosis may play an important role in the development of chronic obstructive emphysema in this disease.

SUMMARY AND CONCLUSIONS

An analysis was made of the number of patients with well-defined chronic obstructive emphysema who gave a history of "chronic bronchitis," as defined by the British workers which antedates their present complaint of dyspnea.

During the ten years from 1948 to 1958, 3,422 patients were screened at our laboratories by conventional ventilatory function tests. They were indexed under "emphysema" if they had

all of the following: maximal breathing capacity less than 80 per cent of predicted, air velocity index less than 0.8, one-second timed vital capacity less than 70 per cent, residual volume of more than 125 per cent of predicted, and a pulmonary mixing index of more than 1.5 per cent N_2. They were not included if there was marked improvement after bronchodilator aerosol.

Of 1,889 patients who did not have pulmonary tuberculosis, 555 or 29.4 per cent had chronic obstructive emphysema by the above definition. The first 100 records, in alphabetical order, of these 555 emphysema patients were examined. The ratio of men to women was 3.76:1. Fourteen per cent had "dry emphysema" without cough, expectoration, or a history of pulmonary infections; 18 per cent had "wet emphysema" with cough, expectoration, and often acute exacerbations all beginning some time *after* onset of exertional dyspnea; and 68 per cent gave a history typical for chronic bronchitis as defined in Great Britain; that is, progressively increasing productive cough, worse in the winter and worse in the morning, *antedating* the onset of dyspnea by three or more years.

Sixty-nine per cent had smoked 10 cigarettes or more per day for ten years or more. The incidence of smokers was the same in all three groups of patients.

Among the 1,533 patients with pulmonary tuberculosis, about one-half were referred because of varying degrees of dyspnea. Of these, 61 per cent had chronic obstructive emphysema. The remaining 780 patients were studied routinely, irrespective of their clinical status, in preparation for surgery. In this nonselected group, 42.6 per cent had evidence of obstructive emphysema. Results are reported of a sanatorium survey of 200 medical patients with moderately to far advanced tuberculosis of more than two years' duration. In this group 16.5 per cent showed evidence of respiratory obstruction with a relatively normal stroke volume, and 44 per cent showed changes typical of chronic obstructive emphysema.

This preliminary survey suggests that in two-thirds of patients with chronic obstructive emphysema documented by physiologic studies, chronic bronchitis may well be the primary, if not the sole, etiologic factor. In pulmonary tuberculosis, specific chronic bronchitis is a more likely etiologic factor in the development of obstructive emphysema than overdistention of the lung tissue adjacent to areas of contracture.

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A SURGICAL APPROACH TO PULMONARY EMPHYSEMA[1]

OTTO C. BRANTIGAN, EUGENE MUELLER, AND MILTON B. KRESS

Introduction

After eight years of study by trial and error methods, an operation has evolved designed to restore a well-known physiologic mechanism that has, for the most part, been lost in the patient with idiopathic, hypertrophic, obstructive pulmonary emphysema. It is an operation directed at restoration of a physiologic principle. It is not concerned with the removal of pathologic tissue.

Analysis of Problem

Definition of emphysema: Emphysema is characterized by physiologic airway obstruction which affects expiration more than inspiration; pathologically organic obstruction cannot be demonstrated. Physiologic measurements reveal obstruction to the airway and reduced ventilation. By ausculatory methods the breath sounds are found to range from diminished to absent sounds over the entire chest. The breath sounds further diminish or disappear after cough. The thorax may be barrel-shaped. Roentgenographically the lung markings appear reduced from normal (figure 108). The anteroposterior diameter of the chest is increased. The diaphragms are flattened and often steplike at their attachment to the costal margin. The condition manifests itself to the patient by a varying degree of dyspnea, morning cough, and expectoration of a dram or two of tenacious secretion. Frequently, the patient gradually loses weight. Usually the disease slowly becomes progressively worse. This type of pulmonary emphysema should be distinguished from the secondary type, the type caused by some specific disease such as silicosis, generalized fibrosis resulting from a specific infection such as tuberculosis, extensive bronchiectasis, and other conditions. The operation to be described will not be of benefit in the secondary type of pulmonary emphysema.

An analysis of a few generally accepted fundamental pathologic changes in the emphysematous lung, a statement concerning the anatomic structure of the normal bronchiole, and a review of a well-known physiologic mechanism that normally holds open the bronchioles, will be presented. If these fundamental observations can be accepted as correct and true, it is easy to show how the disturbed physiologic mechanism can be altered by operation.

In idiopathic, hypertrophic, obstructive pulmonary emphysema the disease is generalized in the lungs. There are no areas of normal lung tissue; however, all areas of the lung are not involved equally by the pathologic process (figure 109). The areas of the lung most involved pathologically are usually located about the periphery of the lobe. The areas of lung tissue with the most extensive pathologic changes are functionless as respiratory tissue. The emphysematous lung has lost its elasticity to a greater or less degree, and this is true whether or not definite changes can be demonstrated in the elastic tissue. Vascular changes with degeneration of the capillary beds are noted when lung tissue is destroyed to the greatest degree by the pathologic process, and this causes a greater or lesser degree of pulmonary hypertension. The lung volume is greater than normal (1–3) (figure 109). The thorax in the emphysematous patient is more or less fixed in a state of full inspiration, and the diaphragms are lowered or depressed.

Anatomically, there is no cartilage in the bronchioles. There is not enough elastic tissue in their walls to hold them open as a rubber tube is held open (figure 110). The bronchioles are collapsible. They are collapsed or closed tubes unless they are held expanded by some physiologic mechanism. The bronchioles in emphysema are grossly and microscopically not unlike those that are normal. Perhaps some evidence of infection and hypertrophy of the mucous membrane can be detected. The elastic tissue in their walls resembles that in the normal walls. The bronchioles from the emphysematous lung are collapsible tubes similar to those in the normal lung and they will not remain open unless held open by a normal physiologic force or mechanism.

The normal physiologic mechanism holding open the bronchioles in health or disease is the elastic collapsible lung held in an expanded state by a closed pleural space and the rigid chest wall. The elasticity of the expanded lung

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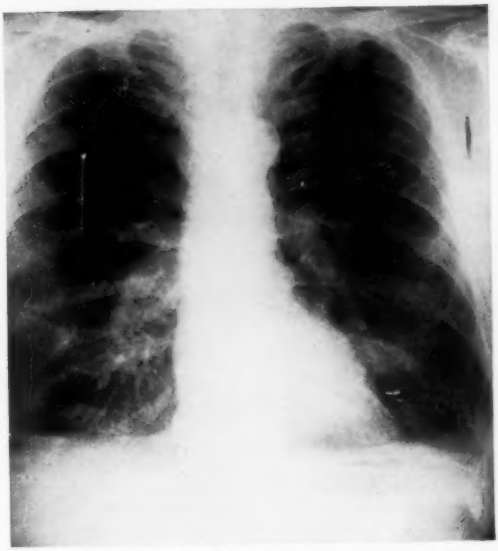

FIG. 108. A roentgenogram of a 50-year-old man with idiopathic, hypertrophic, obstructive pulmonary emphysema.

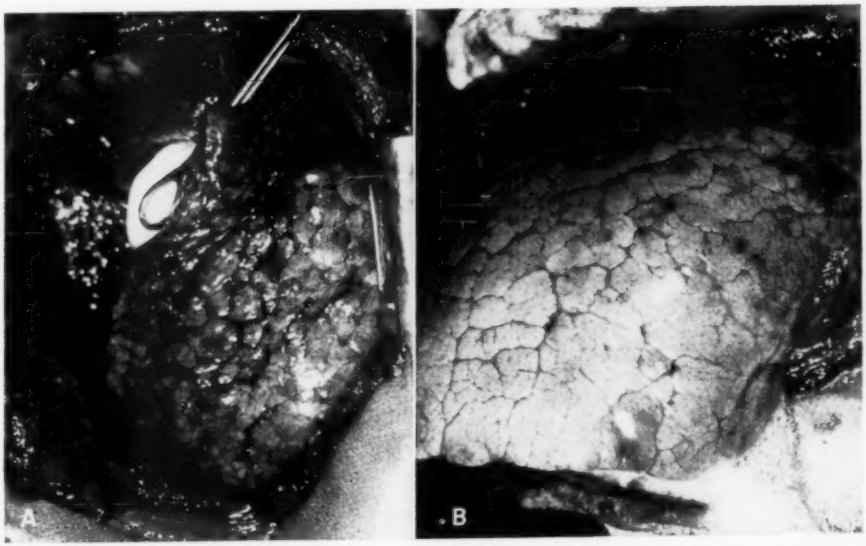

FIG. 109. These photographs were taken at operation for pulmonary emphysema. (Left) There is an absence of blebs or bullae. However, all areas of the lung are not equally involved in the generalized pulmonary pathologic process. (Right) This photograph illustrates the voluminous character of the idiopathic, hypertrophic, obstructive emphysematous lung at the time of operation.

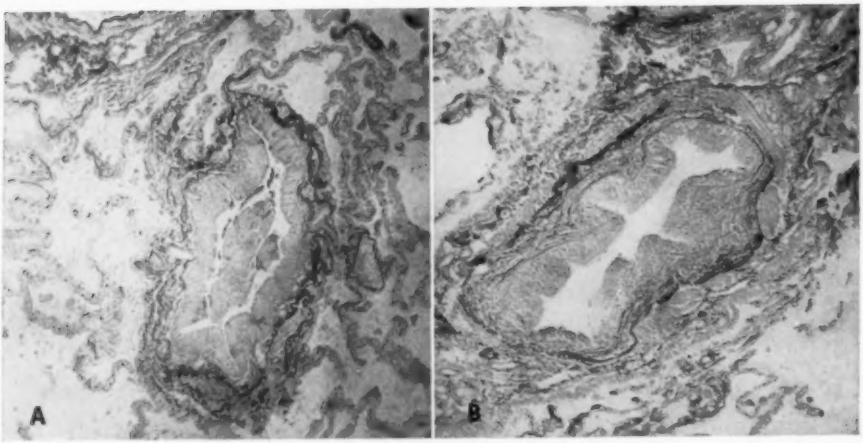

FIG. 110. The photomicrographs are of bronchioles: (Left) from normal lung and (Right) from idiopathic, hypertrophic, obstructive pulmonary emphysema. Little difference is noted in the two specimens and no cartilage is seen in them. There is not enough elastic tissue or elastic fibers in their walls to hold them open in the same manner as a rubber tube is held open.

tissue is then transmitted to the pliable bronchioles, which are held open by a circumferential elastic pull (figure 111). This is the physiologic process that causes the bronchi to enlarge normally in diameter and lengthen on inspiration and to decrease in diameter and shorten on expiration. The elastic circumferential pull is never lost in the normal lung.

The condition in pulmonary emphysema is similar to the stuffing of an inelastic lung of 6,000 or 7,000 cc. volume into a pleural space of 5,000 cc. capacity (figure 111). The emphysematous lung has lost its elasticity to a greater or less degree. The circumferential pull holding open the bronchioles is greatly impaired. It may be completely lost on expiration, but by maintaining the chest in a state of complete inspiration the patient is able to retain some of the mechanism of circumferential pull, thus holding open the bronchioles on forced inspiration. However, this pull is lost on expiration, which accounts for the greater obstruction to air flow on expiration.

METHOD OF OPERATION

The operation for pulmonary emphysema is directed at a reduction in lung volume by resection of the most useless and functionless areas of lung tissue (figure 112). The lung volume is reduced to the capacity that fits the volume of the pleural space on full expiration. Thus, the impaired physiologic mechanism of circumferential pull upon the bronchioles is restored to some degree. When the emphysematous lung of reduced volume is held expanded by the closed pleural space and rigid chest wall after operation, it cannot be returned to normal since the elasticity of the emphysematous lung has been impaired. In reducing the lung volume by removal of useless areas of lung tissue, no functioning lung tissue is lost to the patient. It is conceivable that some less diseased areas of lung that have been held collapsed may be put into use. There is also an establishment of the more nearly normal intrathoracic negative pressure that will aid cardiac action. To avoid the removal of functioning lung tissue, segmental or lobar resection is cautiously avoided. The reduction in lung volume also brings about a dome-shaped higher diaphragm which permits it to function more efficiently. The thoracic cage, if still flexible, assumes a more nearly normal position. These effects afford better ventilation as shown by a definite improvement in breath sounds and an increased exercise ability of the patient.

The second part of the operation consists of lung denervation (figure 113). The parasympathetic fibers are removed by resecting and ligating all branches of the vagus nerve from the superior aperture of the thorax to the inferior pulmonary vein; of course, the recurrent laryngeal nerve is spared. A local sympathectomy is carried out by periarterial stripping of the pulmonary artery, peribronchial stripping of the main bronchus, and perivenous stripping of the two pulmonary veins. In addition, the pulmonary ligament is removed. The bronchial arteries, which are usually normal or small in size, are resected in

order to remove the sympathetic nerves they carry to the lung. The thoracic sympathetic trunk and the thoracic sympathetic ganglia are not disturbed. Thus, a localized sympathectomy is accomplished.

The physiology or function of the nerves to the lungs is not clearly understood, but it is believed that at least three results are obtained from denervation. The most noticeable and important result is the drying up of the bronchial gland secretion which causes the meager tenacious sputum that produces so much distressing cough on awakening. Denervation relieves any associated bronchial spasm and it has a tendency to aid capillary blood flow and thus help to reduce pulmonary hypertension (4).

The surgical procedure must be carried out on both sides of the chest. If one side is worse than the other, that side is done first. If not, the larger or right side is operated upon first. The second side is not operated upon until at least three months after the first operation, thus allowing time for maximal benefits from the first operation.

The surgery has been performed on 33 patients. The youngest was sixteen years of age and the oldest sixty-nine. This report brings up to date the series previously reported (5–7). There have been 6 postoperative deaths. At least 2 were technical errors, and the last death was due to kidney failure in the 69-year-old patient. Although this patient was a severe pulmonary cripple before operation, there was no important respiratory problem postoperatively. There have been no deaths following the operation on the second side. This probably indicates how much better surgical risks the patients become after the first operation, or perhaps it is evidence of the improvement in pulmonary function.

Pulmonary function studies have not been done on all of the patients, and this is especially true with those operated upon early in the series. There have been patients in whom there was no change in the measurable pulmonary function after surgery. However, in these same patients the breath sounds and the exercise tolerance were greatly improved. The cough was relieved and the patient was able to return to a gainful occupation without medication. In others there has been definite measurable improvement. For example, in one patient a maximal preoperative breathing capacity of 18 was 33 after surgery. This patient's improvement and respiratory ability apparently exceeded the figures of function as stated. An improvement in pulmonary function can be demonstrated routinely

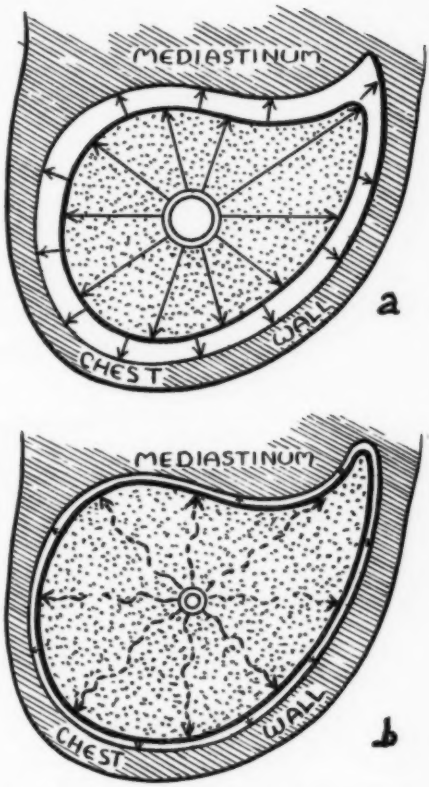

FIG. 111(*a*). The drawing indicates an elastic lung held expanded by a closed pleural space and a rigid chest wall. The elastic lung held expanded by the rigid chest wall exerts its elastic pull upon the intrapulmonary collapsible bronchioles in a circumferential manner, thus holding them open.

(*b*) An illustration of a voluminous emphysematous lung of 6,000- or 7,000-cc. capacity contained in a pleural space of perhaps 5,000-cc. capacity. The voluminous emphysematous lung has lost much of its elasticity. The elastic circumferential pull upon the bronchioles is lost to a greater or less degree. The bronchioles are not held open.

By resecting functionally useless areas the emphysematous lung can be reduced in volume to fit or equal the pleural capacity in full expiration, thus restoring, as in (*a*), the normal physiologic factor of circumferential pull upon the bronchioles. With the bronchioles held open, air is permitted an easier flow in and out of the alveoli, thus providing ventilation. There is a tendency also to restore the normal negative intrathoracic negative pressure, which may be of some aid to cardiac action.

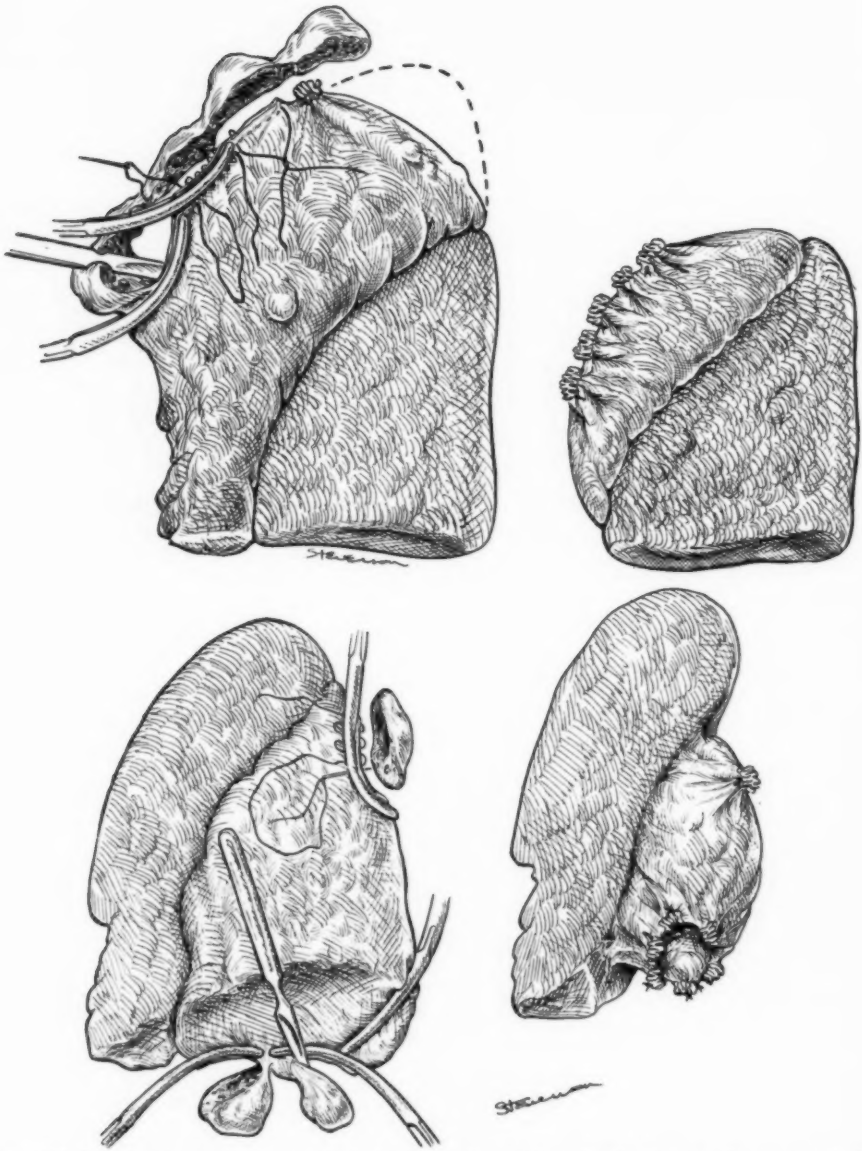

FIG. 112. The drawings present a method of reducing lung volume by the clamp and suture method. The functionless areas of lung tissue are resected for the reduction in lung volume. Fortunately, the functionally useless areas are usually at the periphery of the lobe. Segmental resection or lobectomy should at all times be avoided. It should always be remembered that excision of pathologic tissue is not the purpose of the operation. Instead, the operation is designed to restore the normal physiologic method of circumferential pull, holding open the collapsible bronchioles. Reduction in lung volume is accomplished as much by constriction of the running atraumatic chromic catgut suture as by volume of lung tissue removed. The lung volume is reduced sufficiently to equal the capacity of the pleural space in expiration. Reduction in lung volume below capacity of the expiratory phase of the pleural space must be avoided since the remaining lung will not expand to fill the pleural space as in a normal lung. Thus, air leaks from the emphysematous lung may not be controlled.

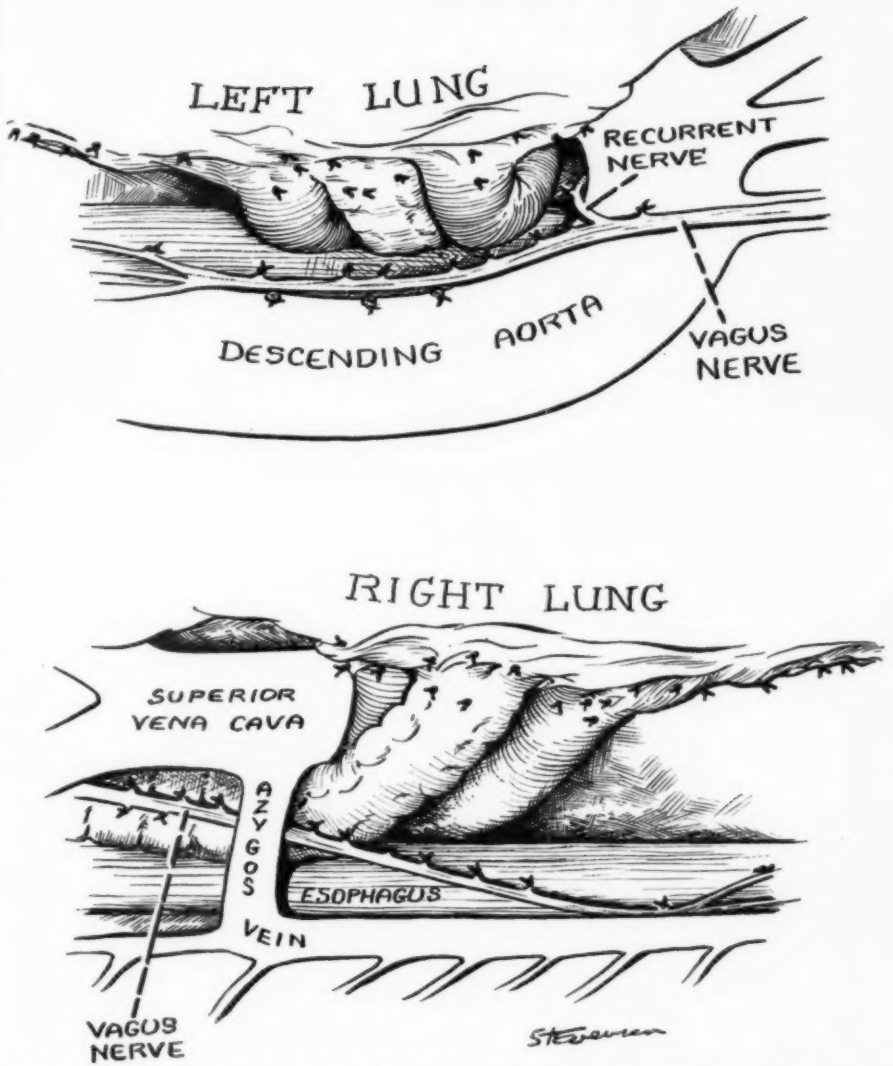

FIG. 113. The drawings illustrate the method of denervation of the lung. All branches of the vagus nerve are excised and ligated from the superior aperture of the thorax to the level of the inferior pulmonary vein. Of course, the recurrent laryngeal nerve is spared. The thoracic sympathetic ganglia and trunk are not disturbed. A localized sympathectomy is accomplished by means of periarterial stripping of the pulmonary artery, perivenous stripping of the two pulmonary veins, peribronchial stripping of the main bronchus, and resection of the bronchial arteries. The pulmonary ligament is divided. When the denervation is completed the lung is attached by the bare pulmonary artery, the bare bronchus, and the two bare pulmonary veins.

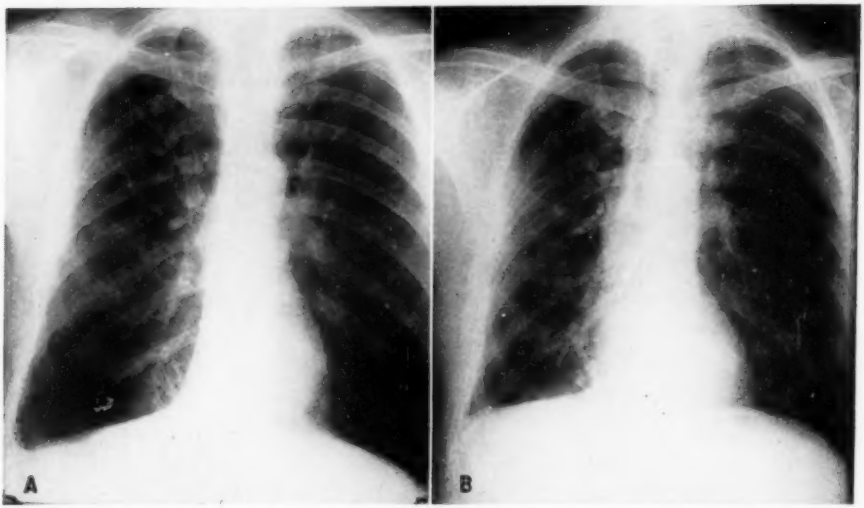

FIG. 114. The roentgenograms are of a 51-year old man, taken three months after the emphysema operation (reduction of lung volume and denervation) was performed on the right lung. They were taken before operating on the left lung: (Left) lung is in full inspiration; (Right) lung is in complete expiration. The mediastinum shifts to the right side. The difference in the size of the right lung can be noted (Left) in inspiration and (Right) on expiration. This difference in size indicates aeration or ventilation. Air moves in and out of the right lung. The left unoperated lung remains about the same size, indicating that air is slowly entering and leaving it.

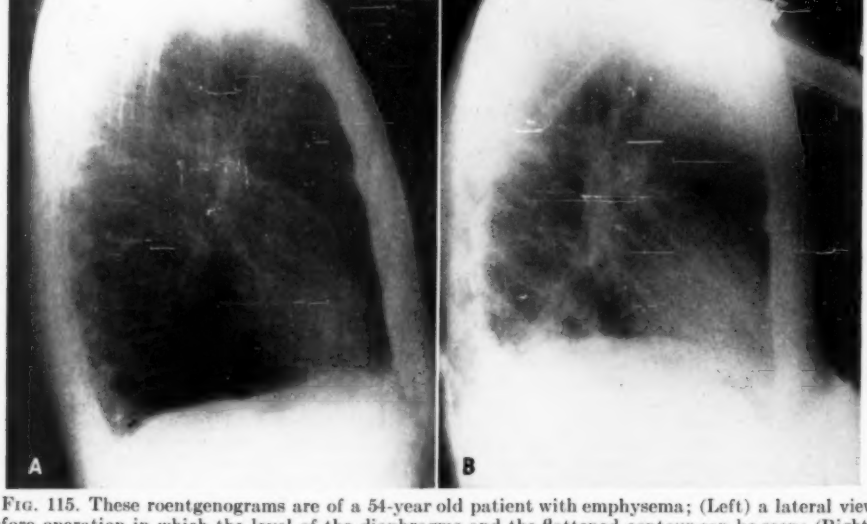

FIG. 115. These roentgenograms are of a 54-year old patient with emphysema; (Left) a lateral view before operation in which the level of the diaphragms and the flattened contour can be seen; (Right) a lateral view of the same patient after bilateral operation for emphysema. It may be observed that the diaphragms are about two vertebrae higher, and there is a normal upward convexity to the diaphragm.

by roentgenographic studies. After the first stage there was a shift of the mediastinum to the operated side on expiration (figure 114), indicating the ventilation of the operated side. This was confirmed by good breath sounds which were easily audible. There was an elevation of the diaphragm (figure 115). This was usually more pronounced on the lateral roentgenographic view.

All patients who survived operation have been helped, except one who died four months after surgery on one side of the chest. He seemingly received no benefit from the operation. However, careful postoperative observation was denied the present writers and, therefore, no pertinent comment or conclusion can be reached. All others have been improved. Those who were not retired have returned to a gainful occupation and in most instances required no medication. In addition to the patient just described, 3 have died since recovery from surgery. These 3 patients died from causes not directly attributable to the pulmonary emphysema, seemingly from sudden coronary arterial disease. One of these patients died four years postoperatively at the age of sixty-one while on a world tour. He maintained the increased respiratory ability until his death.

Discussion

There have been many unexpected developments in this rather limited study. The apparent arrest of the usual progression of the disease has been the most pleasant surprise. The patient with the longest postoperative interval, about eight years, showed no signs of progression of his disease. Surely the disease will continue its relentless progression in spite of surgery, but progression after surgery is not evident in this small series. Cohn (8) said:

> If disability in pulmonary emphysema is closely related to airway obstruction, then a simple and frequently repeated procedure consistently capable of producing an increase in airway obstruction must be presumed to have a harmful effect.

Laennec (9) wrote in 1781 that in pulmonary emphysema air makes its escape slower than from a normal lung:

> . . . and it is quite intelligible that if we can diminish the intensity of the cause which keeps up the habitual distension of the cells we may in the end hope that these will be actually lessened in volume.

Since surgery seems to retard or arrest progression of the disease, perhaps it is the best indication of the improvement to be derived from the operation.

Benefit from the operation was indicated from the beginning of the work. However, an understanding of the mechanism has been evident only in the last eighteen to twenty-four months. Formerly only patients with severe respiratory distress were accepted for surgery. It was clear from the earliest efforts that, if the patient did not obtain definite improvement in respiratory ability, he would not survive the operation. It was observed that the emphysematous patient tolerated the emphysema operation with less difficulty than he would an appendectomy or a cholecystectomy.

It is now believed that the scope of the study should be expanded to accept idiopathic, hypertrophic, obstructive pulmonary emphysematous patients who are not in the terminal or near-terminal state of the disease, to which it was limited in the past. This theory is based upon the conviction that an increase in respiratory function of the patient can be predicted after operation and routinely repeated, and upon the evidence that the natural progression of the disease is definitely delayed.

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General Discussion

Dr. Miller: The points raised by Dr. Brantigan certainly are of great interest and deserve very careful consideration, not only with regard to the therapy of emphysema, but also with regard to other aspects of emphysema such as etiology and exact definition. Our experience is in many ways similar to that described by Dr. Brantigan, but there are certain differences in technique and in results which need careful evaluation.

Our approach, technically, has been based on the fact that almost all cases of emphysema have areas of lung which are relatively less involved than others, the most extensive involvement usually being peripheral. These areas of "dead air space" markedly decrease the ability of lesser involved areas to function efficiently. The total volume within the thorax is increased by the dead air space, and the diaphragms are depressed downward to a point where they lack adequate additional room for downward descent on inspiration.

Surgical obliteration of this dead air space is what we have attempted to accomplish in all of our cases, great care being taken to avoid all areas that have functional value. The technique that we have used varies from one case to another, it being our opinion that simple plication is sometimes indicated, whereas in other cases the clamping and resection of emphysematous areas as described by Dr. Brantigan are better adapted. We have never found it necessary to do a lobectomy or even a segmental resection per se. Whatever procedure is done, meticulous attention is paid to control of air leaks. This, on occasion, has taken longer than any other phase of the operation, but we think it has proved to be very important.

The question of denervation of the lung has not seemed to us to be sufficiently well understood to justify making this procedure a part of every operation in emphysema. We have denervated the hilus in several cases, however, but only on the basis of having first established definite preoperative evidence of bronchospasm relieved by bronchodilators.

We have not been in favor of cutting the bronchial artery, and we have not seen the indication for carrying out parietal pleurectomy as described by others. Multiple-tube drainage has been used, and in some instances we have done an elective tracheotomy. Excellent teamwork with the anesthesia and the medical departments has undoubtedly accounted for a large part of the success we have had thus far in that we have had no mortality, and all of our patients except one have shown definite subjective and some objective improvement. The degree of this improvement has varied considerably, the subjective improvement always turning out to be more marked than what could be determined objectively by careful postoperative pulmonary function studies. In general, however, it can be said that the total lung volume and the residual air are reduced. Vital capacity is increased. The diaphragm on the operated side is able to elevate to a higher level, thus, of course, playing a very important part in whatever ventilatory improvement has resulted in these cases.

With regard to results, we have been able to follow all of our patients carefully, including postoperative function studies, and our impression, thus far, differs from Dr. Brantigan's in that the majority of our patients have shown a slow but definite trend toward gradual progression of their emphysema.

Finally, we believe that it is of great importance to have the medical men who are interested in emphysema come to the operating room and personally inspect and help evaluate the findings in each case in the hope that this will play a part in solving some of the puzzles that impede significant progress in learning more about emphysema.

Dr. Childs: The kind of study that Dr. Brantigan is doing, and which we are also attempting to do, may elucidate some of the pathogenetic factors of emphysema. We realize that this is not an investigation of the beginning of the disease, but in many emphysematous people there comes a point of decompensation, a point when these people become disabled, and I think a study of this decompensation is in order. I believe that I can confirm all of Dr. Brantigan's findings and I must say that my impression has been that at the end stages of this disease, when physiologic disability is at its utmost, there is a definite change, more in one part of the lung than in the other. I don't believe that this generalized disease affects all parts of the lung equally. With proper pulmonary function studies, we may determine whether or not increasing the space in the chest will allow the lung to reassume a bronchial configuration which will permit its emptying properly.

In this regard I would like to emphasize one thing: that, when the patient who has a maximal breathing capacity between 17 and 30 gets in trouble with bronchitis, he is in bad trouble because he cannot empty his lungs of the natural secretions which accumulate there. Perhaps the reason for this is that he has lost his "draft." There is no sweeping current of air, and therefore

he cannot get rid of the secretions. We have had this point brought home to us in the postoperative care of these patients. It has been necessary to breathe for them, either manually or with some automatic apparatus, for several days and remove their secretions manually.

DR. BUKANTZ: I am particularly interested to learn from both Drs. McLean and Liebow that even cases of "dry" emphysema may reveal large amounts of intrabronchial mucus. Two of Dr. Brantigan's figures also revealed considerable intrabronchial accumulation of mucus, to the presence of which he paid little attention, remarking only about the possible role of nerves in controlling this. The questions that one might raise concerning the role of this mucus are whether or not it represents an excess amount of normal material, whether it represents a little abnormal material, or whether it is normal material produced in normal amounts but for the removal of which normal mechanisms are at fault.

A first approach to answering these questions consisted of an attempt to characterize mucus chemically. On histologic examination, mucus from such patients takes a polysaccharide stain. Chemical and immunologic studies revealed this to be a mucopolysaccharide closely resembling blood group substance. Such sputum was found to be fully antigenic in rabbits. Rabbits immunized with sputum in sterile suspension yield positive intradermal skin test reactions (of the delayed type) after an appropriate period after immunization, when tested with blood group *A* and *B* substance of commercial origin, which you will recall comes from the horse and the hog. These skin tests, therefore, represent the sort of specific blood-group-substance reactions engendered by the injection of sputum into the rabbit. Antisera obtained from rabbits immunized with sputum from a group *A* subject contain agglutinins for human erythrocytes of the homologous type in high titer, but only low titers of cross-reacting agglutinins for *B* and *O* erythrocytes. This immunologic approach seemed to offer some help in characterizing this material. These methods may also provide a means of histochemical study by which the mechanisms of production may be ascertained, as well as permit some study of the genetic factors which are surely involved in these diseases.

Studies were performed with the Ouchterlony double-diffusion technique in which the upper well contained serum from a rabbit immunized with human sputum and the lower wells contained sputa from homologous as well as heterologous subjects. By heterologous I mean sputa from a *B* subject and an *O* subject. Multiple precipitating lines appeared in these wells, some of which revealed distinct reactions of identity; in other words, there are some kinds of both specific and common antigens which are present in the sputum from the emphysematous or asthmatic subject. In short, it may be pertinent to know the blood group of the individual with emphysema. Such a relationship has been intensively studied in peptic ulcer and in carcinoma of the stomach. Finally, I hope the tissue fixers will try to fix the material so that some of this mucus remains and we can get some concept of what it looks like in all patients suffering from this disease.

DR. JOSEPH TOMASHEFSKI (Columbus, Ohio): I would like to insert a word of caution concerning the interpretation of functional impairments as indicative of pulmonary emphysema. This is especially true in patients with industrial exposure, such as silicotic patients, and patients with tuberculosis.

This morning we saw from Dr. Bates' presentation that the use of the diffusing capacity is not infallible in the diagnosis of emphysema. Dr. Bates also pointed out that it is important to do repeated studies on these patients before that diagnosis is firmly established. The diagnosis of emphysema should depend upon the correlation of the clinical findings, the pathologic findings, and the functional findings. If these do not agree, then an attempt should be made to determine the reason.

We all ought to beware of a premature diagnosis of emphysema. I have seen a number of patients labeled emphysematous who after careful evaluation showed no evidence of the disease. Iatrogenic emphysema like iatrogenic heart disease can be produced. The symptom of dyspnea on exertion should be a prerequisite before the patient is informed that emphysema is present.

We have been quite interested at the Ohio Tuberculosis Hospital in the relation of tuberculosis to emphysema, and find in routine evaluation of tuberculous patients that there is a combined obstructive-restrictive type of abnormality, and that the obstructive variety is found most frequently in the patients with advanced pulmonary tuberculosis. This combined obstructive-restrictive factor is manifested by reduced vital capacity, poor three-second vital capacity, reduced maximal breathing capacity, and a discrepancy between the vital capacity and the maximal breathing capacity. I agree with Dr. Gaensler that the use of the residual volume/total lung capacity ratio should be condemned. We noted that this ratio is increased to a greater extent in patients with advanced tuberculosis than in the minimal group. I believe that this is due primarily to a decrease in the total lung capacity, although this is not always so, and occasionally one finds a patient with far advanced tuberculosis and clas-

sical chronic obstructive emphysema. Arterial oxygen unsaturation is not common in patients with tuberculosis unless other functional abnormalities are also present. In 40 patients with tuberculosis examined consecutively, there were 24 with far advanced disease; only 10 of these showed arterial oxygen saturation below 95 per cent. The unsaturation was of only a slight degree, never being less than 90 per cent. In the moderately advanced group, only 2 of 13 patients had a saturation below 95 per cent. No patients with minimal tuberculosis manifested evidence of unsaturation.

It is our opinion that tuberculosis does not cause chronic obstructive pulmonary emphysema. On the other hand, the type of emphysema seen in the tuberculous patient differs from the type of emphysema seen in the nontuberculous. In tuberculosis, emphysema is due chiefly to overdistention of the lung, resulting from a loss of lung tissue. Before making a diagnosis of chronic obstructive emphysema in a patient with tuberculosis, one should take into consideration the age and the presence of chronic bronchitis, because, as Dr. Gaensler mentioned, patients with tuberculosis also frequently have an associated bronchitis.

Dr. Williams: We have been interested in abnormalities of cardiopulmonary function in emphysema in contrast to those in bronchial asthma. The mean maximal midexpiratory flow rate in emphysema is a great deal lower than in asthma, whereas the range in asthma is much greater than that in emphysema. The asthmatic patient may have a low maximal midexpiratory flow rate on occasion, but at times it will be high. This appears to be one distinguishing characteristic between these two diseases The vital capacity is reduced in both, but a bit more in emphysema. The diffusing capacity, particularly the exercise diffusing capacity which is a more valid measurement, appears also to distinguish between asthma and emphysema. Although the resting diffusing capacity may be quite low in asthma, the range is great, and the exercise diffusing capacity seems to provide a clear-cut distinction between the two diseases. For a definition of emphysema we require an exercise diffusing capacity of less than 12 cc. of carbon monoxide per minute per mm. of mercury. The hemodynamic studies are not greatly different in these two diseases. The pulmonary arterial pressure is elevated, slightly more in emphysema. The cardiac index in emphysema is usually normal at rest, slightly elevated in the asthmatic at rest, and normal during exercise. Serial studies may show that there is no particular deterioration of pulmonary functions in a given individual with emphysema. Pulmonary hypertension may not seem to increase, the diffusing capacity may not decrease, and ventilatory function may stay relatively constant. This does not appear to be a common course in emphysema, but it points out that emphysema is not necessarily a relentlessly progressive disease, and suggests the possibility that emphysema develops all of a sudden and is not gradually progressive in onset.

A survey of employees of Grasslands Hospital was conducted in an attempt to detect emphysema and thus define the incidence of this disease in a sample population. The employees were surveyed with spirograms and each individual who had an MMF less than 1 liter per second was retested. When the MMF was consistently less than 1.0 liter per second, the diffusing capacity was measured. If this was less than 12 cc. of carbon monoxide per minute per mm. of mercury, the patient was called emphysematous. In this population there were two cases of emphysema so defined, and these people both fitted in the group of men more than forty years old who smoked, giving an incidence of 1.5 per cent in this particular population.

Dr. Bates: I am very glad indeed that the perennial difficulty of distrust across both sides of the Atlantic with respect to chronic bronchitis is rapidly ending. It has lasted far too long. The people here have believed that the British have a fixation about coughing, and the British can't understand why the people on this side of the Atlantic keep on saying there isn't much chronic bronchitis. I'm sure the solution of the problem is not dramatic. It just needed some conversation.

As far as definition is concerned, it is abundantly clear from the epidemiologic work coming out of the midlands of England that chronic bronchitis in those areas is extremely common and that emphysema in those areas is also extremely common. It is practically true to say that no physician there ever sees emphysema without a long history of preceding cough. Perhaps occasionally he does see one, but he's swamped by hundreds of others he sees who have coughed, who cough in his office, and who have coughed years beforehand. This picture will not necessarily be true in Denver, Boston, or New York, and the fact that in those cities people don't cough like that and still get emphysema is of course a very important observation. But let's recognize that there are marked differences in incidence of chronic bronchitis and that the physicians and physiologists on both sides of the Atlantic are good observers, and in general their observations are right for their own locality.

The solution to this problem will come only when we can swap information among ourselves in an intelligent manner. It's been most distressing to sit here and to have the findings on 10 cases of emphysema from New York, on 10 complicated

mathematical analyses of flow rate in emphysema from Bethesda, on surgical results on a few more, on one or two from me, and the pathologists talking about still others. We urgently need a method so that we have some idea about the particular patients who take part in the very elaborate investigations done. We will get nowhere until we know the characteristics of the particular patients each investgator has studied. The type of clinical description the average journal will accept is totally inadequate, and one of the points I hope will be raised later is whether we can or cannot reach any sort of useful method of swapping that basic information.

I am delighted to see Dr. Brantigan stressing that, although emphysema appears to be generalized on the plain anteroposterior film, it is not often so when the lung is examined at operation, a highly significant observation. I agree entirely with him. This is a new finding as far as I am concerned, and we picked it up only because of the use of tomograms.

In reply to Dr. Tomashefski, it's the exception that proves the rule. It took me two years to find the man with bronchospasm and a low diffusing capacity, and the data are as Dr. Williams shows. The diffusing capacity does discriminate, except for the exception I showed, which is why I showed it. As far as the smoking problem is concerned, in a paper in the *British Medical Journal* relating to a survey of men in the sixth decade of life from the point of view of chronic bronchitis and emphysema, the incidence of chronic bronchitis and emphysema in non-smoking men was 15 per cent. In smokers it was very much higher. The incidence among smokers was also closely related to economic status. This is a significant observation and may explain why one doctor with an office practice made up of wealthy people may get a different impression than a physician from a city hospital. If that's true over here, the epidemiologist must consider the socio-economic classification when considering incidence of chronic bronchitis in smokers.

We need extensive data on epidemiology controlled with maximal midexpiratory flow rates. We need a close study of apparent early cases of emphysema and very long-term follow-up observations on them. And finally, we urgently need a method of intercommunication between specialized laboratories so that at least we have some idea of the particular subjects chosen for study in detailed and elaborate investigation.

Dr. John F. Marchand (New York, New York): The air pollution problem is very likely to be a useful thing to explore in terms of the etiology of emphysema. When I was quite small, I used to complain when I found a cockroach or other foreign body in my food, but I was reassured that before one dies he eats a peck of dirt. Well now, eating it doesn't matter so much but breathing it perhaps does, and we do breathe a lot of "dirt" and other pollutants, each of which may have some specific effect on lung tissue. There isn't any other tissue in the body into which we pour as much "dirt" as we do into our lungs; a lot of it stays there, and the effect of this is that tissue reactions of various incompatibility types may occur. I think this gives us an important lead to follow in working out the pathogenesis and natural history of emphysema.

Dr. Cherniack: I am sure Dr. Gaensler didn't mean to imply that chronic bronchitis occurred only in the humid areas and only in the areas with heavy industry fumes, because we all know it occurs elsewhere. We have a very high incidence of emphysema in Canada, and it is my impression that 65 to 70 per cent of the patients with emphysema have clinical histories consistent with chronic bronchitis. And we find, too, as Dr. Gaensler did, especially on the Veterans Hospital wards, that almost everybody was "gassed" in 1918.

Dr. H. Dumont Clark (Denver, Colorado): In relation to the etiology of emphysema, consideration should be given to chronic and subacute inflammations of the *upper* respiratory tract, which includes the nose, paranasal sinuses, and pharynx. The mouth, while not strictly a segment of the upper respiratory tract, can be considered a part of it for purposes of this discussion. The fact that there is a sizable proportion of the population who have chronic or subacute inflammation of the upper respiratory tract as a result of the common viral diseases is well recognized. One of the results of such inflammation is the production of mucopurulent secretions which may contain bacterial and other toxins. These secretions are often present for years. Secretions or other material from the upper respiratory tract commonly enter the bronchial tree by direct extension, frequently when the individual is asleep. Such secretions may form mucous plugs in the smaller bronchi and, if they contain irritating substances or bacteria, they may produce localized areas of bronchial inflammation or infection.

Another mechanism by which the upper respiratory tract may influence the lower respiratory tract is through the lymphatics. The tracheobronchial lymphatics have a direct connection with the deep lymphatics of the neck, which in turn drain the upper respiratory tract. Whether there is much retrograde flow from the deep lymphatics of the neck to those of the tracheobronchial tree may be questioned.

Finally, it should be noted that the individual who is prone to upper respiratory tract infection

tends to have more bronchial infection than the average individual. In this connection there is often a problem of allergy, and upper respiratory infections can lead to allergic manifestations in the bronchi. The implications of the above mechanisms in the etiology and pathogenesis of emphysema are obvious.

DR. GAENSLER: Surgeons have a wonderful opportunity to contribute to our understanding of the pathogenesis of emphysema. I think that this opportunity has been entirely missed by nearly everyone who has done surgery for emphysema. There are a variety of things that have been done, whether ill-advised or not, concerning the nerves, the volume of the lung, the excision of blebs, and so forth. If one reviews the literature, one finds first a confusion of terminology which is so fantastic in most papers that one cannot get anything out of it. For example, one sees roentgenograms of what is obviously a simple cyst in a person with a maximal breathing capacity of 160 liters per minute, determined only after operation. This is described as improvement. There are no studies that I am aware of in which patients were studied, operated upon, and at due intervals studied again. The fact that half the patients after operation are better is not too meaningful; almost anything that can be done for a patient with emphysema is likely to result in some improvement for some weeks. I think that, if we do such surgery, we should at least contribute by performing very complete studies.

The other thing is that Dr. Brantigan has said he believes that emphysema is largely a local disease that appears here and there, whereas internists generally believe that it is a diffuse disease. I think the reason is that, if it is a diffuse disease, the internist is not likely to refer the patient to the surgeon; but, if one can see little bullous areas here and there that might be amenable to a knife, the patient is apt to be referred to a surgeon.

DR. RADFORD: The Committee on Terminology has rightfully stressed the fact that in dealing with emphysema we are dealing with a pathologic entity. My own message to this group was that one cannot consider elasticity as a simple stretching of fibers, but must consider the surface properties of the lungs in characterizing the state of inflation. I am personally quite unhappy with the fixation technique proposed for use in the future in studying the disease.

DR. C. J. MARTIN (Seattle, Washington): I agree with Dr. Brantigan that there are no "skyhooks" in the lung which pull out or support in an open fashion small bronchioles that do not have the support within their walls. The walls of the small bronchioles are not pulled out, but rather pushed out by atmospheric pressure; in an elastic or plastic body there simply cannot be supporting strings that hold open various areas.

DR. BRANTIGAN: Emphysema is admittedly a generalized pulmonary disease, but all areas are not equally involved. The areas that are more involved (from the pathologic point of view) are probably completely useless as respiratory tissue. This is not the same as saying that emphysema is a localized disease.

Regarding mucus, the story that I frequently, if not always, get from my patients is that they have the worst time raising sputum in the morning. This indicates to me that the small bronchioles are not held open by something; I merely say that they don't have cartilage in them. The theory has been advanced for many years that these bronchioles are held open by an elastic pull. Maybe that's all wrong.

AN EMPHYSEMA REGISTRY[1]

GEORGE C. BOWER

My thesis is quite simple: we need to devise a method by which we can classify persons with emphysema so that information from various investigators can be pooled. The purpose of an emphysema registry is to effect a horizontal study of the disease, in order to define its course, complications, response to therapy, and clinical-physiologic-pathologic correlations.

Is diffuse obstructive emphysema as seen in Denver the same type of disease as seen in Boston, New York, or London? And is the background and development of the disease the same in various locales? One approach to this question is to compare data—clinical, physiologic, and pathologic—from separate centers. In this way we may be able to discover certain differences in the disease as seen, for example, in industrial versus nonindustrial groups, urban versus rural populations, sea-level versus high-altitude inhabitants, smokers versus non-smokers, men versus women, and chronic bronchitics versus non-bronchitics. Because no one investigator can collect extensive data on such diverse groups, it would appear practical to devise a classification which would lend itself to the pooling and analysis of data.

Dr. Ebert has pointed out that the term "emphysema" is often applied to a variety of problems in clinical medicine. Thus, the definition of the disease becomes important in order that we all study the same process. It might be argued that we don't know what emphysema is except in the far advanced case or unless the pathologist examines the lungs. Arbitrary selection of persons for study, either on clinical or physiologic grounds, could conceivably lead to mistaken concepts about the disease because we are likely to omit from study those who have mild or unrecognizable forms of the disease. The real problem in selection relates to the person with early or incipient emphysema; chronic bronchitics and heavy cigarette smokers are good candidates for prospective studies. Retrospective analysis of the classical advanced case will probably tell us nothing of the early development of the disease or of ways in which early disease might be detected. Can we diagnose emphysema "early" and can this be done by simple ventilatory tests? A problem here is the defining of "normal" values, and it may be that our ideas of normal have been prejudiced by the inclusion of "healthy" smokers with non-smokers.

We include for study persons who have breathlessness on exertion in the absence of heart disease (excluding cor pulmonale). Those too incapacitated, or with pneumoconioses, significant tuberculosis, or bronchiectasis or large bullae are excluded from this study. Thorough medical examination, followed by fluoroscopic and roentgenographic study, ventilatory and lung volume tests, resting and exercise blood gas and diffusing capacity determinations, is performed. A significant number of patients undergo cardiac catheterization. The tests are repeated at eight- to twelve-month intervals.

A set of numbers and letters can be used to classify a given patient.

Sex: M F Age____

Age onset of dyspnea____

I. Occupation before onset: (a) hard work (b) other

II. Smoking habits (cigarettes/day times years): (c) 400 plus (d) 200–400 (e) less than 200 (f) 0

III. Family history of bronchitis, asthma, emphysema: (g) yes (h) no

IV. Bronchospasm, i.e., wheeze, "asthma," response to bronchodilators: (i) yes (j) no

V. Chronic bronchitis (occasionally cough and sputum for at least two years): (k) yes (l) no

VI. Cough: (m) chronic productive several years before dyspnea (n) same with or after dyspnea (p) dry cough several years before dyspnea (q) same with or after dyspnea (r) no cough

VII. Degree of dyspnea: (s) minimal (t) slight (u) moderate (v) severe

VIII. Weight loss: (w) more than 15% usual weight (x) less than 15%

IX. Peptic ulcer symptoms: (A) yes (B) no

X. Heart failure: (C) yes (D) no

XI. Polycythemia: (E) Hematocrit more than 60% (F) 50–60 (G) less than 50

[1] From the University of Colorado School of Medicine, Denver 20, Colorado.

XII. Roentgenogram: (H) general and local abnormalities (I) general (J) not diagnostic
XIII. MBC: (K) less than 30 L./min. (L) 30–70 (M) 70 plus
XIV. MMF: (N) less than 0.5 L./sec. (P) 0.5–1.5 (Q) 1.5 plus
XV. RV/predicted RV: (R) more than 3 (S) 2.0–3 (T) less than 2.0
XVI. Mixing efficiency: (U) very bad (V) poor (W) fair
XVII. CO_2 retention: (X) severe (Y) moderate (Z) absent
XVIII. Art. O_2Hb sat.: (1) normal (2) abnormal at exercise only (3) abnormal at rest and exercise
XIX. Exercise D_{co}: (4) less than 6 (5) 6–12 (6) 12 plus
XX. Exercise ventilatory equivalent: (7) over 45; (8) 30–45; (9) under 30

"0" indicates no test done. Any patient can be described in terms of a series of letters and numbers.

Some preliminary observations on a group of 100 emphysematous patients can be offered. The group appears to fall into several categories: those with histories consistent with chronic bronchitis; those with chronic unproductive cough, often attributed to cigarettes and rarely subject to repeated apparent infection; and finally, the most unusual group, those who do not cough until after the onset of dyspnea or perhaps never at all.

Dr. Williams noted that the disease is not invariably progressive. On the other hand, some patients show sudden onset and rapid progression; this is likely to occur in a younger male who smokes heavily and who has no history of chronic bronchitis but who does have a "cigarette cough."

Emphysema is a common disease among hard-working farmers and ranchers living in a rather dry climate in Colorado.

Women we have studied appear to have more evidence of chronic infection than males with similar physiologic abnormalities. The former are possibly younger at onset of dyspnea and for some reason do not show marked weight loss so common in men.

About 96 of 100 patients we have studied were smokers of cigarettes in moderate to large quantities.

General Discussion

Dr. Bates: We cannot and should not attempt to impose any uniformity on the investigations, or the system of record-keeping, or on anything that any department wishes to use. That's not the point of an emphysema registry, so far as I have visualized it. The point of an emphysema registry, which is not the word I would have chosen, is as follows. If we could classify a case of emphysema, even in broad outline, by a simple set of letters, as I believe we can—and as the people I have corresponded with believe we can at this stage—then the collection of this information, even if very incomplete in some centers, would be of real comparative value. If, in other words, somebody has been thoroughly studied clinically and physiologically, he could be compared with a man of fifty in London who has had ten years of chronic cough in whom we know only the MMF, and there could be useful comparisons made, even with centers collecting very few data. It is my belief that useful information can be collected. It must be virtually no trouble to anybody, and nobody must be encouraged or cajoled into changing methods or the extent of his study, or anything to fit in with it. That seems to be an essential requirement.

A pathologist will produce sections and one day we will know the pulmonary function defects; we will know something of the people Dr. Brantigan sees, and this seems to me a hopeful avenue of approach, particularly in advance of the epidemiologic studies, which are quite certainly going to descend on us now in quantity. This is the time to get some very broad classifications so that we can make some sense of the combined data.

Dr. Williams: I would like to make one other suggestion: that we focus our attention on the *development* of this disease which we can now recognize physiologically, clinically, and pathologically, and that we search out and study over a period of years people with what we think may eventually be emphysema.

There are other categories which might be fruitful: one is chronic bronchitis; another is the patient with shortness of breath of unexplained cause; another is the patient with tuberculosis. Apparently emphysema is common in this disease and, if we could study people with acute tuberculosis and follow them over the years, we might determine something about the sequential development of disorder of pulmonary function. The final group includes those with "holes" in their lungs that Dr. Fishman has talked about, some of whom seem to develop emphysema.

SUMMARY OF THE CONFERENCE[1]

RICHARD V. EBERT

I think it will be a little difficult to summarize this conference. One of its strengths is that so many divergent views were presented. It might be pointed out that the purpose of the conference was to obtain information which will eventually lead to the prevention of emphysema, the alleviation of suffering of the patient, or the prolongation of his life. In order for us to attain this objective, more information is necessary. It is hoped that the conference will define those areas where investigation will be suitable and profitable. I think it is quite clear from the discussion that one of the defects in the area of emphysema has been lack of communication between people working on various segments of the problem. I think most of us have been interested in one specific aspect of the disease and have utilized certain tools of investigation to elucidate one area of emphysema. There has been a general lack of interest in, or understanding of, the total picture. I think this conference has gone a long way toward bringing people together and allowing them to see the broader aspects of this disease state.

One of the things that interested me most—perhaps because I knew the least about it—was the discussion of the anatomy of the lung. I think it is quite clear that, if we are to produce a hypothesis regarding the etiology of emphysema, this must be based on the normal structure of the lung because emphysema is essentially a distortion of the normal architecture. Moreover, an understanding of the normal architecture of the lung is essential to an understanding of the physiology of the normal lung, and hence the physiology of emphysema. Both Dr. Loosli and Dr. Krahl gave lucid descriptions of the normal anatomy of the lung. They pointed out the extreme complexity of the terminal unit of the lung, that is, the respiratory bronchiole, the alveolar duct, the alveolar sac, and the alveoli which arise from all of these structures. I think it is quite certain that the pathology of emphysema is intimately related to these terminal structures, although the exact portion that is involved is less clear.

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Dr. Loosli gave a most interesting discussion of the development of the elastic fibers of the lung and pointed out that this development is not complete at birth but continues thereafter. Moreover, he pointed out a most interesting aspect of the anatomy: these fibers gather in a node about the openings of the alveoli; this apparently serves to strengthen the structure of the respiratory bronchiole and of the alveoli that are associated with it. The anatomists also showed us in a most dramatic manner the beautiful arrangement of the capillaries about the alveoli, forming an intricate network, which is designed to enable exchange of gas between the alveolar air and the blood.

What can we derive from these anatomic considerations regarding the function of the lung and the development of pulmonary emphysema? I think first that we must consider the lung essentially as a mechanism for exchange of oxygen and carbon dioxide, between the blood flowing through the pulmonary capillaries and the alveolar air. For this to occur there must be an appropriate exchange of alveolar air with the air outside of the individual. There are two important factors involved in the exchange of air which are relevant to the structure of the lung. One of these is the elastic properties of the terminal structure which I have just described or, to put it perhaps more correctly, the pressure-volume relationships of this structure. The second is the resistance to airflow in the tracheobronchial tree and in this structure itself.

Obviously, the elastic properties of this structure, or its pressure-volume relationships, are determined by many things. Most of us immediately think of the elastic fibers as contributing chiefly to this. I do not know whether that is correct or not. Dr. Radford has emphasized the importance of the surface properties of the film of fluid lining the alveoli. The elastic fibers undoubtedly play an important role. I think that the description of the manner in which these fibers surround the alveoli and associate themselves with the elastic fibers of the vascular system help us understand how these fibers contribute to the elastic properties of these structures.

There are other factors involved in the pressure-volume relationship, such as the muscular fibers that are associated with respiratory bronchioles and, perhaps, as was pointed out by Dr. Krahl, the epithelial cells which line the alveoli may in themselves have elastic properties. In any case, the elastic properties or pressure-volume relationships are a summation of the properties of all of these structures. In addition, it was pointed out that the geometric structure of the alveoli, the respiratory bronchiole, and the alveolar duct probably plays an important role in this pressure-volume relationship. We are not dealing with a sphere but rather with a very complex structure. It expands in a manner which resembles an accordion. Both Dr. Dayman and Dr. Radford commented on this.

The anatomy of the lung will also ultimately cast light on the pressure-flow relationships. The resistance to airflow is intimately related to the diameter and to the geometry of the air passages. As a demonstration of this, the work of Rohrer may be recalled. By defining the anatomy of the tracheobronchial tree, he was able to calculate the resistance to airflow in the normal lung in a rather remarkable manner. Our concepts of pressure-volume and pressure-flow relationships must, in the last analysis, be based on the anatomic structure of the lung. The maximal expiratory airflow, which Dr. Fry commented on, is intimately related to these pressure-volume and pressure-flow relationships. In addition, Dr. Fry pointed out that the compliance of the bronchiolar structures is another parameter which must be taken into consideration.

In addition to those factors which influence ventilation of the lung, the distribution of the capillaries to the various alveoli must be considered. The distribution of blood to various portions of the lung is related to the exchange of carbon dioxide and oxygen between air and blood. One thing that might be appropriate to mention is the fact that perhaps it is not so extraordinary that people have emphysema and difficulty with ventilation and perfusion, but rather that the normal lung functions in such an efficient manner. For normal distribution of air to occur, each of these respiratory units must have approximately the same pressure-volume and pressure-flow relationships. If they differed in their pressure-volume or pressure-flow relationships, some units would receive more air than others, and there would be unequal ventilation. The remarkable thing is the uniformity of the structure of the lung which apparently permits equal ventilation of all of these terminal structures in the various portions of the lung. Moreover, as was pointed out by Dr. Briscoe, in the normal lung there must be a constant relationship between ventilation and perfusion with blood for each one of these structures. So that perhaps it is more remarkable that the normal lung has such constancy in these pressure-flow, pressure-volume, and perfusion relationships than that the lungs of a patient with emphysema have an abnormal relationship.

Finally, a word should be said about the dissolution of the structure of the lung which occurs in patients with emphysema. It is not entirely clear how this dissolution of lung substance occurs. Dissolution may not be the proper term. The formation of holes might be a better term, but it is quite evident that in some way the normal structure is distorted. Dr. Pierce pointed out that the structural proteins of the lung, the collagen and elastin, actually form a skeleton in the lung which maintains the ordinary structure. The capillaries and epithelium are laid down upon this basic skeleton of the lung. This skeleton is distorted in patients with emphysema. Perhaps if we understood what led to this distortion, we might know more about the pathogenesis of the disease.

One of the most interesting aspects of the conference was the presentations of the pathologists. I think that one of the real advances in an understanding of emphysema has resulted from the improvement in pathologic techniques. As I mentioned in my earlier discussion, one of the trying things to the clinician in the past has been difficulty in clinical-pathologic correlation because of the lack of interest of many pathologists in the details of the disease. The pathologists now are taking a lead in this field. All of us here apparently believe that a knowledge of the structure of the lung in emphysema is essential to our understanding of the disease and that we have great need for more clinical-pathologic correlation. The advances in technique which were described here two days ago have permitted such clinical-pathologic correlation. I would like to make a very strong plea that all people interested in this disease attempt to document this clinical-pathologic correlation.

In the past, those of us who were primarily interested in pulmonary function studies were not able to document the relationship of our studies to the pathology of the disease, particularly to

the pathology in a quantitative sense. It has been brought out that the disease does not necessarily involve all parts of both lungs equally, but may be localized to a varying degree. If we have a knowledge of the exact pathology of the lung and can correlate this with the clinical picture and with the physiologic findings, I think we will be in a position to make much more exact conclusions regarding the disease. I hope that, if this conference is ever repeated, such studies will be available. I think we all appreciate the difficulty in performing such studies and the need for cooperation.

The pathologists illustrated the varied nature of the disease with their beautiful studies obtained by studying distended lungs sectioned in various manners. They pointed out that we cannot consider emphysema as a single entity. There may be simply local areas of emphysema or holes in the lung adjacent to areas of fibrosis. Whether this should be considered as part of the disease process most of us are talking about clinically is a problem. Second, the entity of centrilobular emphysema has been emphasized, both at this conference and in recent publications. Most of us were not familiar with this pathologic entity until recently, and the question has arisen as to its clinical significance.

I talked informally with Dr. McLean and Dr. Wyatt, and I do not think that we have enough data as yet to relate the pathology to a specific clinical picture either in terms of disability or in terms of alteration in pulmonary function. It is absolutely essential that we obtain this information. Here is a large area that is practically untouched. The more diffuse forms of emphysema I think are familiar to all of us, but I am sure that we gained something by looking at the figures because of the diversity of the pathologic changes that were exhibited. In some lungs there seemed to be almost total destruction of anything resembling normal architecture. I rather liked the description used by one of the pathologists, that this resembled a chambered nautilus. In other lungs the disease seemed more localized, often in the upper portions of the lobes. This is in rather striking contrast to bronchiectasis which tends to be localized, of course, in the dependent portions of the lung.

Dr. Liebow gave a very helpful discussion of both the bronchial and the pulmonary circulation in emphysema. He pointed out that there is actual withering or disappearance of the small pulmonary vessels in the area of emphysema, a fact which fits in with the physiologic data and with the angiograms and tomograms that Dr. Bates demonstrated today. He also pointed out that, while there may be changes in the bronchial circulation, if anything, the bronchial circulation is increased. He could supply no data which would support the concept that emphysema is the result of ischemia of the lung from atrophy or narrowing of the bronchial arteries. I think after his presentation it would be difficult to support this theory.

One more thing I wish to mention regarding the pathologic studies is that all of the pathologists agreed, in response to my question, that there was no evidence of diffuse narrowing of the bronchioles in emphysema. There were localized areas of narrowing, but they did not think that the extent of narrowing visible on their microscopic sections of the lung was adequate to explain the increased resistance to airflow which is observed clinically. This I think is of some importance because it means that the resistance to airflow must be explained on some other basis. The fact that the pathologists did not observe narrowing, of course, does not imply that the caliber of the bronchioles is not decreased as a result of edema or spasm, but at least there appears to be no uniform structural narrowing. It was pointed out that perhaps we must take into account the geometry of the entire system of air spaces in explaining this resistance to airflow.

There was an excellent discussion of the physiology of the lung. I have already pointed out that Dr. Fry described the mechanics of ventilation in terms of three parameters. These were the pressure-volume characteristics of the lung, the pressure-flow relationships or resistance and, finally, the compliance of the bronchiole. He did this by creating a mathematical and physical model which enabled him to explain the maximal expiratory flow curves obtained from patients with emphysema and from normal persons. The usefulness of such mathematical and physical models was discussed. Dr. Briscoe also pointed out the inhomogeneity of alveolar ventilation in patients with emphysema. He also was of the opinion that it was necessary to postulate an inhomogeneity in perfusion of the various alveoli or respiratory units in the lung in order to explain the defects in gas exchange. Finally, Dr. Fowler and Dr. Fritts emphasized that we not only have to consider the lung itself in emphysema but also the muscles, the afferent and efferent nerves, and the respira-

tory center. They pointed out the complexities that are involved in the whole process of ventilation and indicated means by which these complexities could be explored.

I would like to spend a little time on some of the questions that have been raised by the conference and point out some of the areas in which further studies are indicated. One area I have already mentioned. This is clinical-pathologic correlation. If we are to base our definition of emphysema on the change in structure of the lung, we must have this information in order to communicate with each other. Second, it is obvious that we need more studies regarding the epidemiology of emphysema.

Most of us have been interested in one very specific aspect of emphysema and few of us have taken a broad view of emphysema. I will have to admit that I did the same thing as Dr. Gaensler. I pulled out a group of our records, examined them, and found them to be quite inadequate in regard to possible etiologic factors. Certainly the approach that has been used in the past to determine what percentage of patients smoke and what percentage of patients have a chronic cough will not be adequate. It is going to be necessary to carry on broader epidemiologic studies which will give us a definitive answer in the various areas that have been mentioned. The relation of chronic bronchitis to emphysema, the relation of pollution of the atmosphere, the relation of smoking, the relation of other chronic inflammatory diseases, will have to be determined by very carefully planned studies with exact criteria for the diagnosis of emphysema. If possible, such studies should be controled by pathologic examination of the lungs.

I have perhaps not emphasized the physiology of the lung adequately because this is the area in which most of the work has been done. I believe that the studies in physiology have contributed enormously to our clinical understanding of the disease, to the management of the patient on the ward, and to the clinical recognition of the disease. However, I am rather doubtful that the physiologic studies by themselves will elucidate the pathogenesis of the disease or allow us to develop methods of prevention of the disease. They can be used as tools in defining the disease and permit such epidemiologic studies to be sharply defined.

There is need for a method of experimental production of emphysema in animals. Dr. Eiseman last night discussed the various methods that have been used in the past. There has been no uniform method accepted by the various workers in the field which will produce a disease in animals which resembles emphysema in human beings. There have been a number of hypotheses as to the etiology and pathogenesis of emphysema suggested at this meeting. Perhaps the chief one is that emphysema follows bronchiolitis with air trapping, overdistention of the alveoli, destruction of their substance, and the formation of large air spaces. This is the mechanism that was suggested by Dr. McLean. He will be the first to admit, I believe, that is an hypothesis. Certainly, it would be of great advantage if this mechanism could be validated by a study in experimental animals with the production of a disease like emphysema. There are many other hypotheses which need testing. One is that there is a defect in elastic tissue associated with aging and influenced by hormonal effects or hereditary influences. Unfortunately, there are very few data to support this hypothesis. If we could have further information of an experimental nature it would advance our understanding of emphysema.

POSTSCRIPT TO THE "FIRST" ASPEN CONFERENCE[1]

ROGER S. MITCHELL, CHARLES HOUSTON, AND GILES F. FILLEY

As was anticipated, the cause of emphysema was not reported at the Conference on Research in Emphysema at Aspen, Colorado, in June, 1958. It was, however, a very happy culmination of all sorts of preparations by virtually all (116 registrants) who were there.

One of the happiest events was something intangible at the time—a different and interesting, if not entirely new, method of conducting a scientific conference covering a central theme.

Today one hears on all sides criticism of conventional medical meetings—too long, poor audiovisual aids, too wordy, poor moderators, poor planning, but most of all, *too little time for discussion* and/or *too little good discussion*.

The participants and opening discussors at Aspen were asked to abstract their remarks in advance—which most of them did—for transmission to all participants about ten days before the conference. Everyone was asked in addition to propose a definition of our central theme, emphysema. Some 15 or so responded in time, and these contributions were also circulated.

As a consequence of this advance exchange of information, most participants were somewhat prepared for discussion. This was particularly pertinent because of the numerous disciplines represented and because so many experts in their fields were previously poorly informed of available information in other fields. An obvious fault in our planning, in retrospect, was that still too little time was allotted for discussion. This could have been circumvented if fewer topics had been assigned, as many had urged. But all of those topics discussed, and even more, should properly have at least been introduced at this conference, in the minds of others.

Time could have been saved for discussion, without cutting down on the number of topics, by requesting all who presented papers and had prepared abstracts for circulation in advance to confine their opening remarks at the Conference to a five-minute summary of their prepared talks, using a very few key slides for illustration, plus any new observations between the time of preparation of the manuscript and the day of the meeting.

This technique of conducting such a scientific meeting has precedence in the Faraday Society in Great Britain and at the Symposium on Tuberculosis in Infancy and Childhood held at the National Jewish Hospital in Denver, Colorado, in November, 1956.

It is doubtful whether this technique would lend itself to a meeting on various topics unless they could be organized appropriately into cohesive subdivisions. It is also doubtful whether meetings of more than 50 to 100 persons could be conducted in this way unless the actively participating group was held to an inner circle of no more than 25 to 35 surrounded by an audience of *non*-participants.

Important topics not covered adequately at the conference should not be overlooked. These include upper respiratory infections, tracheobronchial cartilaginous disorders, and kyphoscoliosis, and their relationship to emphysema. Air pollution was barely mentioned. And Dr. Albert Lansing, who was to tell what electron microscopy of the lung reveals, at the last moment was unable to attend.

In short, the First Aspen Conference succeeded, we believe, in identifying our knowledge as well as our ignorance regarding emphysema. It set the stage, we hope, to stimulate and even coordinate research in the field. It enabled people to meet other people known to each other only through published scientific articles. It produced an admirable crossing of interdisciplinary lines (between morphologists, physiologists, and clinicians, in particular). The groundwork was also laid for an International Congress on Emphysema, probably in 1961, again at Aspen, we hope.

Other tentative plans for future Aspen Conferences on Research in Emphysema include the following subjects: mechanics of breathing, dyspnea, air pollution, "chronic bronchitis," and man's adaptation to hypoxia.

[1] From Colorado Foundation for Research in Tuberculosis; and University of Colorado School of Medicine, Denver 20, Colorado.